BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

09/943,037

(12) UK Patent Application (19) GB (11) 2 061 913 A

(21) Application No 7937788
(22) Date of filing 31 Oct 1979
(43) Application published
20 May 1981
(51) INT CL³
C07C 101/00
A61K 31/00
C07C 97/10 103/00
(52) Domestic classification
C2C 1173 1174 1175 1176 1177 1178 1179 1182 1183 1186 1341 1371 1386 1410 1530 1532 1560 1672 200 202 215 220 221 222 225 226 227 22X 22Y 236 246 250 251 252 253 256 25Y 270 271 280 281 282 292 29Y 305 30Y 311 313 314 316 31Y 322 326 32Y 338 339 342 34Y 350 351 355 35X 35Y 360 361 362 364 366 367 368 36Y 385 394 395 396 397 39Y 440 456 45Y 490 491 510 52Y 560 583 591 593 60Y 612 613 620 623 624 625 628 62X 62Y 633 635 638 645 648 652 655 658 65X 660 662 665 666 668 675 67X 680 682 695 699 726 775 776 802 80Y AA KH KJ KK KN LL LS LT LZ NB NJ QE RC RN SC
(56) Documents cited
GB 1406637
GB 1353789
GB 1313789
(58) Field of search
C2C
(71) Applicants
American Cyanamid Company,
Berdan Avenue,
Township of Wayne,
State of New Jersey,
United States of America.
(72) Inventors
Robert Gordon Shepherd
(74) Agents
Tregear Thiemann & Bleach,
Enterprise House,
Isambard Brunel Road,
Portsmouth PO1 2AN,
United Kingdom.

(54) **Novel 2- or 3-[(cycloalkyl- or cycl - alkenyl-substituted)-amino, alkylamin or alkenylamino] phenyl compounds and derivatives**

(57) There are provided novel 2- or 3-[(cycloalkyl- or cycloalkenyl-substituted)-amino, alkylamino or alkenylamino] phenyl compounds and derivatives useful as hypolipidemic and antiatherosclerotic agents.

GB 2 061 913 A

The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

Novel 2- or 3-[cycloalkyl- or cycloalkenyl-substituted)-amino, alkylamino or alkenylamino]phenyl compounds and derivatives

This invention relates to novel 2- or 3-[(cycloalkyl or cycloalkenyl substituted) amino, alkylamino or alkenylamino]phenyl compounds, salts and derivatives of the formula:

wherein Z is:

a) $-\overset{O}{\overset{\|}{C}}-A$

wherein A is selected from the group consisting of hydrogen, hydroxy, loweralkyl, a loweralkoxy group unsubstituted or substituted with one or more moieties selected from the group consisting of hydroxy, carboxyl, carboloweralkoxy, carboxamido, N,N-diloweralkylcarboxamido, cyano, diloweralkylamino, piperazino or polymethyleneimino (ring size 5-8) group; a benzyloxy group unsubstituted or substituted with at least one halogen or carboxy group; a phenoxy moiety unsubstituted or substituted with at least one halogen, carboxy, carboloweralkoxy loweralkyl, carboxamido, loweralkoxy or cyano group; or a 3-pyridyloxy group unsubstituted or substituted with a loweralkyl group, halogen, cyano, carboxyl, carboloweralkoxy, loweralkoxy or hydroxy group; and loweralkyl bearing one or more carboxy, carbaloweralkoxy, carbamoyl, acyl, sulfinyl or sulfonyl groups;

b) $-B-\overset{O}{\overset{\|}{C}}-OE$

wherein B is a saturated or unsaturated lower alkylene group and E is selected from the group consisting of hydrogen, loweralkyl, loweralkoxyethyl, diloweralkylaminoethyl, (mono- or polyhydroxy)-loweralkyl, (mono- or polycarboxy)loweralkyl, (mono- or polycarboxy)hydroxyloweralkyl, allyl, 2,3-epoxypropyl, substituted or unsubstituted (phenyl, benzyl or 3-pyridyl), pyridylmethyl, and tetrahydropyranyl; or

c) $-\overset{O}{\overset{\|}{C}}-N\begin{matrix}R_4\\R_5\end{matrix}$ or $-C(OR_6)=NR_7$

wherein R_4 is selected from the group consisting of hydrogen, carboxyloweralkyl, carboalkoxyloweralkyl, loweralkanoyl, loweralkanesulfonyl, arylsulfonyl, sodium sulfo loweralkyl, sulfo loweralkyl, loweralkenyl, loweralynyl, phenylloweralkyl and ω-hydroxyloweralkyl; r_5 is selected from the group consisting of hydrogen, loweralkyl, hydroxy, loweralkoxy, halooweralkyl, phenyl, carboxyphenyl, chlorophenyl, sodium sulfophenyl, pyridyl, pyridyl loweralkyl, (mono- and polyhydroxy)lower alkyl, ω-loweralkoxyloweralkyl, ω-di(loweralkyl)aminoloweralkyl, ω-piperidinoloweralkyl, ω-pyrrolidinohydroxylower alkyl, amino, loweralkanoylamino, loweralkanesulfonylamino, N-piperidyl, arylsulfonylamino, and 4-loweralkyl-1-piperazino; R_4 and R_5 taken together with the associated nitrogen is selected from the group consisting of pyrrolidino, iperidino, morpholino, hexamethyleneimino, 4-(loweralkyl)piperidino, 4-loweralkyl-1-piperazino, 4-phenylpiperazino, 3-pyrrolinyl, Δ^3-piperidino, 4-(carboethoxy or carboxy)-3-thiazolidinyl and 4-(carboethoxy)-3-oxazolidinyl; R_6 and R_7 are the same or different and are selected from the group consisting of loweralkyl, (mono- and polyhydroxy)loweralkyl, carboxyloweralkyl, sulfo loweralkyl, sodium sulfo loweralkyl, and, when taken together, loweralkylene;

R is selected from the group consisting of hydrogen, or a group convertible *in vivo* thereinto, such as methyl, carobxymethyl, acetyl, succinyl, 1-(sodium sulfo)-loweralkyl, 1-(sodium sulfo)polyhydroxyalkyl and 1,3-*bis*-(sodium sulfo)aralkyl;

n is either zero or one.

y is a divalent radical selected from the group consisting of unbranched or branched C_1-C_{13} alkylene or

alkenylene and is either unsubstituted or substituted with at least one C_1-C_4 alkyl group;

and D is selected from the group consisting of C_3-C_{13} ctcloalkyl or C_4-C_{17} cycloalkenyl and is either unsubstituted or substituted with at least one C_1-C_{13} alkyl, C_4-C_8 cycloalkyl, decahydronaphthyl, methylene, ethylidene, or isopropylidene group;

with the proviso that the total number of carbon atoms in D and Y shall not exceed twenty; and with the further proviso that when n is 1, D is not an unsubstituted cyclopropyl nor a cyclopropyl substituted with at least one C_1-C_{13} alkyl;

and the pharmaceutically acceptable non-toxic acid addition and cationic salts thereof.

Preferred compounds of the invention are as follows:

when n is 1, (Formula IA) Y is a divalent radical selected from the group consisting of branched or unbranched C_1-C_{13} alkylene or alkenylene and is either unsubstituted or substituted with at least one C_1-C_4 alkyl; D is a moiety selected from the group consisting of C_3-C_8 cycloalkyl which is either unsubstituted or substituted with at least one C_1-C_{13} alkyl, a C_5-C_7 cycloalkyl, or a decahydronaphthyl group. with the proviso that D is not an unsubstituted cyclopropyl nor a cyclopropyl substituted with at least one C_1 to C_{13} alkyl, or

Formula IB) Y is a divalent radical selected from the group consisting of branched or unbranched C_1-C_{13} alkylene or alkenylene; and is either unsubstituted or substituted with at least one C_1-C_2 alkyl; and D is a moiety selected from the group consisting of C_4-C_9 cycloalkenyl and is either unsubstituted or substituted with at least one C_1-C_{13} alkyl group; and C_5-C_8 cycloalkyl unsubstituted or substituted with at least one methylene moiety, and/or at least one C_1-C_{13} alkyl;

and when n is 0,

Formula IC) D is a moiety selected from the group consisting of C_4-C_7 cycloalkyl and is either unsubstituted or substituted with at least one C_4-C_7 cycloalkyl, and decahydronaphthalene unsubstituted or substituted with at least one C_1 to C_4 alkyl;

or

Formula ID) D is selected from the group consisting of C_4-C_{16} cycloalkyl substituted with at least one C_1-C_5 alkyl; or

Formula IE) D is a moiety selected from the group consisting of C_4-C_{17} cycloalkenyl which is either unsubstituted or substituted with at least one C_1-C_4 alkyl, and C_4-C_{10} cycloalkyl substituted with a moiety selected from the group consisting of methylene, ethylidene, and isopropylidene and/or at least one C_1-C_4;

with the proviso that the sum of the number of carbon atoms contained in D and Y in Formula I shall not exceed twenty; and the pharmaceutically acceptable acid addition and cationic salts of the above.

The loweralkyl, loweralkenyl, loweralkynyl, loweralkoxy, loweralkanoyl, and loweralkanesulfonyl groups herein contain 1 to 6 carbon atoms and may be branched or unbranched. The number of hydroxyl groups in the polyhydroxy compounds herein are from 2 to 4 hydroxy groups. The number of carboxy groups in the polycarboxy compounds herein are from 2 to 4 carboxyl groups.

Suitable keto-acids and keto-esters contemplated by the present invention are those in which the group A is selected from the group consisting of carboxymethyl; carboxyethyl; 2-carboethoxy-2-propyl; dicarboethoxymethyl; carboethoxyvinyl and the like. Suitable alkanoic, alkenoic and alkynoic acids and esters are those in which the radical Z is selected from the group consisting of 4-carboxybutyl; 2-carboethoxyethyl; 2-carboxyvinyl; 2-carboethoxyethynyl, and the like.

Preferred compounds of the Formula IA are those wherein Y is a divalent radical selected from those consisting of straight-chain C_1-C_{13} alkylene; and still more preferred are the compounds of Formula IA wherein D is a moiety selected from the group consisting of C_5 to C_8 cycyloalkyl. The most preferred compounds of Formula IA are those where Y is a divalent radical selected from the group consisting of a straight chain C_6 to C_8 alkylene.

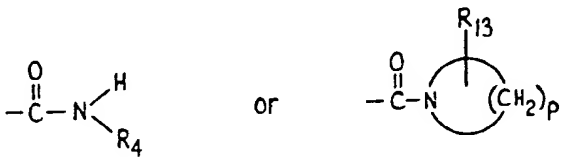
Preferred compounds of Formula IB are those where D is selected from the group consisting of C_5-C_8 cycloalkenyl unsubstituted or substituted with at lease on C_1C_2 alkyl and Y is a divalent radical selected from the group consisting of C_1-C_{13} alkylene; and those compounds wherein Y is a divalent radical selected from the group consisting of C_4-C_{13} alkylene and/or D is C_5 or C_6 cycloalkyl are even more preferred. Additionally preferred embodiments of compounds of Formula IB are those where D is selected from the group consisting of C_5 to C_8 cycloalkyl substituted with a methylene moiety and/or at least one C_1-C_2 alkyl, and Y is $-CH_2-$ or $-CH(CH_3)-$.

Preferred embodiments of the compounds of Formula IC are those where D is selected from the group consisting of C_5-C_6 cycloalkyl which is either unsubstituted or substituted with at lease one C_5-C_6 cycloalkyl, and decahydronapthyl unsubstituted or substituted with at least one C_1-C_4 alkyl.

Preferred compounds of Formula ID are those where D is selected from the group consisting of C_4-C_{16} cycloalkyls which may be unsubstituted or substituted with at lease one C_1-C_5 alkyl and most preferred are those where D is selected from the group consisting of C_5 to C_{12} cycloalkyl.

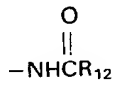
Preferred compounds of Formula IE are those where D is C_4-C_{17} cycloalkenyl or C_4-C_8 cycloalkenyl substituted with at least one C_{1-4} alkyl group; and even more preferred of these is where D is C_5-C_{17} cycloalkenyl and even more preferred of these is where D is C_6 to C_{15} cycloalkenyl. Other preferred compounds of Formula IE are those where D is C_4-C_{10} cycloalkyl substituted with methylene, ethylidene or isopropylidene. Of these the most preferred are those in which D is a C_5-C_{10} cycloalkyl substituted with a methylene.

Additional preferred compounds of Formula I are those wherein Z is:



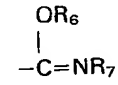
wherein R_4 is a loweralkyl group substituted with at least one hydroxyl group, allyl, propargyl, 2-sulfoethyl, $-(CH_2)_m-COOR_9$ wheren m is 2-4 and R_9 is hydrogen or a loweralkyl group,

wherein R_{12} is a lower-alkyl or aryl group, $-SO_2R_{12}$,



or a $-NHSO_2R_{12}$ group; p is one of the integers 4, 5 and 6 and R_{13} is hydrogen or at least one methyl group.

Also preferred are compounds of Formula I wherein Z is the moiety



wherein R_6 and R_7 are as previously defined.

Additionally preferred compounds of Formula I are those where A is hydroxy; a loweralkoxy group unsubstituted or substituted with one or more carboxy, hydroxyl, diloweralkylamino or polymethyleneimino (ring size 5-8) groups; a benzyloxy or phenoxy group which is unsubstituted or substituted with at least one halogen or carboxyl group; or 3-pyridyloxy.

The invention also pertains to novel compositions of matter useful as antiatherosclerotic agents and to methods of ameliorating atherosclerosis by counteracting hyperlipemia and arterial plaque formation in mammals therewith; the active ingredients of said compositions of matter being the novel 2- or 3-[(cycloalkyl or cycloalkenyl substituted) amino, alkylamino or alkemylamino]phenyl compounds of the present invention. These compounds may be utilized either as such or in the form of a pharmaceutically acceptable salt with an organic or inorganic acid or base. The invention also contemplates a method for lowering serum lipids and for ameliorating atherosclerosis in mammals by the administration of said compounds.

BACKGROUND OF THE INVENTION

Considerable effort has been directed in recent years to obtain substances useful in counteracting the consequences of hyperlipidemia, a condition involving elevated cholesterol, phospholipid and/or triglyceride levels in the blood, and of hyperlipoproteinemia, involving an imbalance of the lipo-proteins. The most serious condition associated with hyperlipidemia and hyperlipoproteinemia is atherosclerosis, a form of arteriosclerosis characterized by lipid accumulation and thickening of the walls of both medium-sized and large arteries such as the aorta. Their walls are thereby weakened and the elasticity and effective internal size of the arteries decreased. Atherosclerosis, the most common cause of coronary artery disease, is of great medical importance since it tends to occlude those arteries supplying blood to the heart muscles and brain, thereby producing permanent damage to these organs. Such damage may lead to ischemic heart disease, congestive heart failure, life-threatening arrhythmias, senility, or stroke. Involvement of leg arteries may lead to gangrene and loss of the limb. It has been known for more than 100 years that cholesterol is a major component of atherosclerotic lesions or plaques. Investigators have been trying to determine the role of cholesterol in lesion initiation and development and also, most importantly, whether lesion formation can be prevented or reversed and enlargement of lesions be slowed to stopped. The earliest lesions are now known to be fatty streaks, largely or cholesterol, which often progress in stages to plaques containing cellular, fibrous and calcified material in addition to the lipids.

The evidence that hyperlipidemia is one of the factors involved in coronary heart disease is very impressive. A most important study carried out in Framingham, Mass. (Gordon and Verter, 1969) in over 5,000 persons for more thant 12 years established a correlation between high concentrations of blood cholesterol and increased risk of heart attack. Although the causes of coronary artery disease are multiple,

one of the most constant factors has been the elevated concentration of lipids in the blood plasma. A combined elevation of cholesterol and triglycerides have been shown (Carlson and Bottiger, 1972) to carry the highest risk of coronary heart disease. The majority of patients with ischemic heart disease or peripheral vascular disease were found to have hyperlipoproteinemia, involving very low-density and/or low-density lipoproteins (Lewis *et al.* 1974).

The reason for most treatment of hyperlipidemia or hyperlipoproteinemia is for arresting, reversing or preventing atherosclerosis. In the past, attempts have been made to lower the level of cholesterol, phospholipids, and trigylcerides in the blood by the oral feeding of various substances which have been generally referred to in the art as hypolipidemic agents or hypocholesteremic adjuvants. Typical of such substances are lecithin, pectin, cottonseed oil, and the mucilaginous substances listed in U.S. Patent No. 3,148,114. In addition, several synthetic hypolipidemic agents are now available, namely, clofibrate, D-thyroxine, cholestyramine, and nicotinic acid [Levy and Frederickson, Postgraduate Medicine *47*, 130 (1970)]. Clofibrate has the undesirable side-effect of causing hypertrophy of the liver in some patients.

The development of agents capable of reducing elevated blood lipids and of favorably altering blood-lipoprotein patterns is considered by medical authorities to be extremely important for the treatment and prevention of atherosclerosis.

Related compounds are the subject of my copending applications Serial No. 884,673, filed March 8, 1978 and Serial No. 8,641, filed February 1, 1979.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are new and novel 2- or 3-[(unsaturated or cyclopropylated alkyl) amino] phenyl compounds and derivatives of Formula I (including Formulas I-A to I-J) which have useful biological and pharmacological properties. No hypolipidemic activity as been reported in the literature for these compounds and they are different in structure from other hypolipidemic agents. The compounds of this invention lower serum-lipid concentrations and also minimize atheroma formation in the aorta. These compounds provide the oral administration required of hypolipidemic agents, which patients usually take for many years. The novel compounds of this invention are adequately and reliably absorbed from the gastrointestinal tract with little, if any, gastrointestinal irritation.

We have now found that certain members of this class of compound can safely and effectively lower both serum-sterols and triglycerides in warm-blooded animals. Such actions on serum lipid components are considered to be very useful in the treatment of atherosclerosis, especially in contrast to available drugs whose action is much more limited. For some time it has been considered desirable to lower serum-lipid levels and to correct lipoprotein imbalance in mammals as a preventive measure against atherosclerosis. The compounds of the present invention do not act by blocking late states of cholesterol biosynthesis and thus do not produce accumulation of intermediates such as desmosterol, as equally undesirable as cholesterol itself. Compounds with the combination of therapeutically favorable characteristics possessed by those of the present invention can be safely administered to warm-blooded mammals for the treatment of hyperlipidemic and atherosclerotic states found in patients with or prone to heart attacks, to peripheral or cerebral vascular disease, and to stroke.

The 2- or 3-[(cycloalkyl or cycloalkenyl substituted) amino, alkylamino or alkenylamino]phenyl compounds salts and derivatives of the present invention are, in general, white crystalline solids having characteristic melting points and absorption spectra. They are soluble in organic solvents such as lower alkanols, chloroform, toluene, dimethylformamide, and the like but are generally not very soluble in water.

The novel compounds of the present invention which are organic bases may be converted to their non-toxic acid-addition or cationic salts with a variety of pharmaceutically acceptable organic and inorganic salt-forming reagents. Thus, acid-addition salts may be formed by admixture of the organic free base in a neutral solvent with one or two equivalents of an acid such as sulfuric, phosphoric, hydrochloric, hydrobromic, trifluoroacetic, citric, tartaric, ascorbic, and the like. Many of the novel compounds of the present invention which contain one or more acidic substituents may be converted to their organic or inorganic cationic salts for therapeutic use. The sodium or potassium salts which are formed in solution in the course of the above described hydrolysis reactions may be isolated as solids by cooling. When it is desirable to purify a compound in the form of acid, the salt is conveniently formed by treating its solution with exactly one equivalent of base and evaporation or lyophylization. Alkaline earth salts are prepared similarly, often using their acetate salts as a conveniently soluble form. Organic base salts such as those of N-methylglucamine are prepared by dissolving equimolar amounts of the acid and the base in hot ethanol or aqueous alcohols and cooling to crystallization.

Many of the novel compounds of the present invention may be prepared by reaction of a 2- or 3-aminophenyl compound with a suitable alkylating agent such as a cycloalkyl or (cycloalkyl)alkyl halide, sulfate, tosylate, or trifluoromethanesulfonate with or without a solvent at 30°C. to 150°C. Appropriate 2- or 3-aminophenyl compounds are, for example, 2- or 3-aminobenzoic acid, methyl 2- or 3-aminobenzoate 2- or 3-aminophenylacetic acid; ethyl 2- or 3-(aminophenyl)acetate; ethyl 3-(2- or 3-aminophenyl)propionate; 2- or 3-aminoacetophenone; 2- or 3-aminobenzaldehyde; 2- or 3-aminocinnamic acid; and methyl 3-(2- or 3-aminophenyl)propenoate. Suitable solvents are lower alkanols, N,N-dimethylformamide, N,N-dimethylacetamide, 1,2-dimethoxyethane, acetonitrile, toluene, benzene, hexamethylphosphoramide and the like. The reaction may be carried out with two equivalents of the 2- or 3-aminophenyl compound or with one

equivalent of the compound plus one equivalent of a base such as an alkali carbonate or bicarbonate or an unreactive organic base such as diisopropylethylamine or alternatively with a catalytic amount of copper powder when a cycloalkyl halide is used as the alkylating agent. Similarly, alkylation of the sodium salt (formed with sodium hydride) of either the amino group of a 2- or 3-aminophenyl compound of the anilide moiety of a 2- or 3-(acetylamino)phenyl compound yields the novel compounds of the invention or an N-acetyl derivative thereof. Removal of the N-acetyl group by conventional hydrolytic methods affords the desired amino compounds.

Alternative methods of preparation of these compounds are by reductive alkylation of a 2- or 3-aminophenyl compound, which may be generated *in situ* by reduction of a 2- or 3-aminophenyl precursor such as a 2- 3-nitrophenyl compound and the like or by a metal hydride reduction of a 2- or 3-(acylamino)phenyl compound. For example, 10-cyclopentyldecanal, 7-cyclohexylheptyl ethyl ketone, or another carbonylalkane and ethyl 2- or 3-aminophenylacetate are reduced under 1-10 atmospheres of hydrogen using an activated metal catalyst or with a metal hydride such as sodium borohydride forming 2- or 3-(10-cyclopentyldecylamino)phenylacetic acid and the like. Diborane reduction of 2- or 3-(cycloalkylalkanoylamino)phenyl compound such as ethyl 2-(11-cyclohexylundecanoylamino)phenylacetate at room temperature or above for 1-6 hours yields the corresponding 2-(cycloalkylalkylamino)phenyl compound such as ethyl 2-(11-cyclohexylundecylamino)phenylacetate. The 2- or 3-(cycloalkylalkanoylamino)phenyl compounds used in these reductions are prepared by acylation of the appropriate 2- or 3-aminophenyl compounds with suitable acylating agents, such as cycloalkylalkanoyl halides. To prepare the 2- or 3-(substituted-amino)phenyl alkenoic and alkynoic acids it is advantageous to form the corresponding alkylchloroimide from the 2- or 3-(acylamino)phenyl compounds using phosphorus oxychloride and base, and then reduce the alkylchloroimide moiety to an alkylamino group with sodium borohydride.

The 2- or 3-(substituted-amino)phenyl compounds of this invention are often prepared from the corresponding 2- or 3-aminophenyl compounds by the sequence involving esterification of any carboxyl groups present with ethanol or methanol in the presence of boron trifluoride etherate, followed by alkylation of the amino function as described above. The free acids are then liberated by hydrolysis of the ester with aqueous alcoholic sodium hydroxide at 80°C. for 2-10 hours followed by acidification. The acids obtained by this procedure may be converted to the corresponding cationic salts. For example, the sodium salt may be prepared by reaction of the benzoic acid with sodium hydroxide in a mixture of ethanol and water. Alternatively, the free acids may be prepared by hydrolysis of the corresponding nitriles of various amides, imidates or oxazolines.

The carboxaldehydes of this invention may be prepared by several methods among which is alkylation of the corresponding acetals as described above followed by hydrolysis of the resulting 2- or 3-(cycloalkylalkylamino)-phenyl compound to the desired aldehyde. Aldehydes may also be prepared by reduction of the appropriate nitriles. For example, treatment of 3-(6-cyclopentylhexylamino)-hydrocinnamonitrile with stannic chloride and anhydrous hydrogen chloride gas, followed by hydrolysis in hot water provides 3-(6-cyclopentylhexylamino)hydrocinamaldehyde. These reductions are also conveniently carried out with hydrides such as diisobutylaluminium hydride.

The α-substituted 2- or 3-(substituted-amino)acetophenones of the invention are prepared by reaction of a derivative of the appropriate benzoic acid, such as 2-(11-cyclohexylundeylamino)benzoyl chloride hydrochloride, with two or more equivalents of the reactive salt of an acidic methylene compound, for example the sodium salt of diethylmalonate. Other benzoic acid derivatives are also suitable for this reaction, such as an N-trifluoroacetyl or N-*tert*-butyloxycarbonyl acid chloride, or a methyl ester of the acid. In some cases the final step in the preparation of the substituted 2- or 3-(substituted amino)acetophenones is the removal of the nitrogen-protecting group. In other cases, hydrolysis of one or more of the ester groups in the acylation product affords an unstable polycarboxylic acid which undergoes decarboxylation to allow the preparation of another acetophenone derivative. For example, the reaction of *tert*-butyl ethyl [2-)11-cyclopentylundecylamino)benzoy)]malonate with trifluoroacetic acid affords ethyl [2-(11-cyclopentylundecylamino)benzoyl]acetate. In other cases, hydrolysis of one or more of the ester groups allows the preparation of the corresponding acid derivative. For example, the hydrolysis of ethyl 3-(6-cyclobutylhexylamino)benzoylacetate yields 3-(6-cyclobutylhexylamino)benzoylacetic acid.

An alternative procedure for preparing certain-substituted-2- or 3-(substituted-amino)acetophenones is alkylation of the corresponding 2- or 3-aminoacetophenones by the methods above. For example, alkylation of methyl 3-(2-amino-benzoyl)propionate with 11-cyclopentylundec-10-enyl bromide yields methyl 3-[2-(11-cyclopentylundec-10-enylamino)benzoyl]-propionate. The related carboxylic acids are then obtained by hydrolysis. Certain acids are particularly useful for the preparation of 2- or 3-(substituted-amino)phenylalkanoic acids by reduction. For example, the Clemmensen or Wolff-Kishner reduction of 3-[2-(6-cyclohexylhexylamino)benzoyl)propionic acid yields 4-[2-(6-cyclohexylhexylamino)phenyl]butyric acid.

The 2- or 3-(substituted-amino)phenylalkenoic acids may be prepared by condensation of the appropriate aldehydes or by dehydration of the corresponding substituted-phenylhydroxyalkanoic acids. For example, ethyl 5-[3-(cyclopentylmethylamino)phenyl]-2,4-pentadienoate is obtained by the Wittig reaction of 3-(cyclopentylmethylamino)benzaldehyde with the Wittig reagent, triethyl 4-phosphonocrotonate. Alternatively, these alkenoic acids are obtained by heating 2- or 3-[N-(10-cyclopentyldecyl-N-

methylamino]benzaldehyde and the like with the sodium salt of the carbanion of ethyl acetate or with a mixture of ethyl acetate, acetic anhydride and potassium acetate. The second method is illustrated by dehydration of ethyl 3-[3-cyclohexylmethylamino)phenyl]-3-hydroxypropionate to yield ethyl 3-cyclohexylmethylaminocinnamate.

The acetylenic analogs are prepared by dehydrobromination of the side-chain vic-dibrominated alkanoic acid. For example, dehydrobromination of ethyl 3-[(2-cyclobutylmethylamino)phenyl]-2,3-dibromopropionate, its isomers or N-acyl analogs or of ethyl 3-[(2-cyclobutylmethylamino)phenyl]-3-bromacrylate yields ethyl 2-(cyclobutylmethylamino)phenylpropiolate. The acetylenic acids are also formed from (2- or 3-substituted-amino)phenylacetylene metal salts by carboxylation with carbon dioxide. The 2- or 3-(substituted-amino)phenylacetylenes are also used by N-acylating with *t*-butyl azidoformate followed by conversion to the lithium acetylide salt and the subsequent reaction of the lithium salt with boron trifluoride etherate in tetrahydrofuran at -20°C. to form *tris*-[(2- or 3-substituted-alkylamino)phenylethynyl]boranes. The tetrahydrofuran solution of the borane is in turn reacted with ethyl diazoacetate, followed by water to yield ethyl 4-[(2- or 3-monoalkylamino)phenyl]-butynoate.

The 2- or 3-(substituted-amino)phenylalkanoic acids, or esters are also prepared by catalytic reduction at 1 to 10 atmospheres of hydrogen of the corresponding alkenoic or alkynoic acid derivatives.

The 2- or 3-(substituted-amino)phenylalkenoic acids and derivatives are prepared by Friedel-Crafts acylation of the N-acyl-N-alkylanilines with the appropriate dicarboxylic acid anhydride or half acid chloride. The substituted-aminobenzoylalkanoic acids or esters, produced by this and other syntheses, may be converted to the corresponding 2-or 3-(substituted-amino)phenylalkanoic acids by reduction with (a) hydrazine and alkali in diethylene glycol at 140° for 3 hours, (b) zinc amalgam and ethanolic hydrochloric acid at 60° for 5 hours, (c) red phosphorus and hydriodic acid, or (d) ketalization with ,3-ethanedithiol followed by Raney nickel desulfurization. The amides of these 2-or 3-(substituted-amino)phenylalkanoic acids are prepared by heating the corresponding 2- or 3-(substituted-amino)phenylalkyl ketones with aqueous alcoholic ammonium polysulfide followed by hydrolysis to yield the acids with the same number of carbon atoms as the ketone. These acids are also prepared by reacting 2- or 3-(N-*t*-butyloxycarbonyl-*N*-substituted-amino)-phenylmagnesium halides with 2-(3-halopropyl)-2-oxazolines, followed by mild acid removal of 2-oxazolinyl and *t*-butoxycarbonyl protecting groups. Similarly, the above Grignard reagent can be reacted with 3-bromotriethylorthopropionate in the presence of dilithiumtetrachlorocuprate to yield the desired acids after removal of the protecting groups from the amino and carboxyl groups.

In certain cases, the unsaturation is introduced at a late stage of the preparation of the 2-or 3-(cycloalkyl unsaturated-alkylamino)benzoic acid derivatives. For example, an alkyl 2- or 3-(cycloalkylhaloalkylamino)-benzoate is dehydrohalogenated to the corresponding olefinic compound.

With certain kinds of substrates for amide formation, it is necessary to form the alkali metal or strong organic base salts of these substrates in order to react them with the various aforementioned acylating forms of the 2- or 3-[(cycloalkyl or cycloalkenyl substituted)amino, alkylamino, or alkenylamino]benzoic and phenylcarboxylic acids. The aminoalkanecarboxylic and aminoalkensulfonic acids are zwitterionic and must be converted to their cationic salts, suitably *in situ*. They may also be used in the form of their esters and then hyrolyzed after amide formation. Certain substrates, which are neutral like the carboxamides or slightly acidic like the alkane or arene sulfonamides, are converted to reactive salts by reaction with sodium hydride or other basic reagents.

Alternatively the free acids may be prepared by hydrolysis of the corresponding nitriles or various amides, imidates or oxazolines. The carboxylic acid moiety may also be generated by oxidation of the corresponding aldehydes, acetophenones, benzyl alcohols, or toluenes, most often with the use of an amine-protecting group such as trifluoroacetyl or *t*-butyloxycarbonyl.

The imidates of the present invention are preferably prepared either by addition of hydroxy compounds to the corresponding nitriles or by alkylation of the corresponding amides, suitably bearing a protecting group on the aromatic amino nitrogen atom in many cases. The addition of alcohols and other hydroxy compounds is carried out under acid catalysis without additional solvent, if possible. Alkylation of the protonated substituted aminoamide may be carried out or the aforementioned amino-protecting groups can be employed. In some cases, simultaneous O-alkylation of the amide and N-alkylation of the aromatic amino moiety can be used to obtain a desired imidate. Intramolecular formation of imidates results from 2-haloethyl and 3-halopropyl amides as well as from 2-hydroxyethyl and 3-hyroxypropyl amides when treated with a condensing agent.

$$\begin{array}{c} R \\ | \end{array}$$

Certain derivatives (−N−) or the aromatic amino nitrogen atom are useful for providing greater solubility, more uniform and reliable intestinal absorption, and for a certain degree of modification of the pharmacology of the compounds of the present invention. Some of these derivatives can be converted to the corresponding N-H forms by the acidity of the stomach or by alkalinity of the small intestine. Others are converted by metabolic processes. The methyl and carboxymethyl derivatives and the like are prepared by the alkylation, reductive alkylation, and acylamino reduction methods above. Derivatives such as the acetyl and succinyl compounds may be prepared using acetyl chloride, acetic anhydride, succinic anhydride, etc. in the presence of pyridine, triethylamine or the like at temperatures moderate enough to avoid acylation of the amide moiety. The 1-(sodium sulfo)alkyl derivatives are obtained by reaction of the 2- or 3-(substituted

amino)phenyl compound with sodium bisulfite and an aliphatic aldehyde, a polyhydroxyaldehyde such as glyceraldehyde or glucose, or cinnamaldehyde in a mixed organic-aqueous medium. In the case of cinnamaldehyde, the di-sulfonate salts result from addition of the bisulfite to the carbon-nitrogen double bond of the anil intermediate as well as to the carbon-carbon double bond of cinnamaldehyde itself.

The novel compounds of the present invention are not only potent hypolipidemic agents but also prevent or diminish the formation or enlargement of arterial plaques in mammals when administered in amounts ranging from about one milligram to about 250 mg. per kilogram of body weight per day. A preferred dosage regimen for optimum results would be from about 5 mg. to about 100 mg. per kilogram of body weight per day, and such dosage units are employed that a total of from about 0.35 gram to about 7.0 grams of the active compound, for a subject of about 70 kg. of body weight, are administered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum theraputic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage of this invention is that the active compound may be administered in a convenient manner by the oral route. The compounds of the present invention exert a more powerful hypocholestermic and antiatherosclerotic effect than the aforementioned adjuvants and synthetic medicaments. It is not known how these novel compounds operate in the blood serum and no theory of why these compounds so operate is advanced. It is not intended that the present invention should be limited to any particular mechanism of action of lowering serum lipids or of ameliorating atherosclerosis, or be limited to compounds acting by only one mechanism.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of the unit. The amount of active ingredient in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage-unit form contains between about 50 and 250 milligrams of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate, a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage-unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl an propyl parabens as preservatives, a dye, and flavouring such as cherry or orange flavor. Of course, any material used in preparing any dosage-unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active ingredients may be incorporated into sustained-release preparations and formulations.

The invention will be described in greater detail in conjunction with the following specific examples.

EXAMPLE 1

Preparation of 2- or 3-[(cyclohexylmethyl)amino]phenylacetic acid

A solution of 6 g. of cyclohexylmethyl bromide and 11.19 g. of ethyl 2- or 3-aminophenyl acetate in 30 ml. of hexamethylphosphoramide is heated in an oil bath for 20 hours. The solution is poured into ice-cold water and extracted several times with diethyl ether. The combined ether extracts are washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to furnish ethyl 2- or 3-cyclohexylmethylaminophenyl acetate as an oil.

The oil is dissolved in 250 ml. of ethanol:water (9:1) containing 9 g of potassium hydroxide and the resulting solution is stirred at the reflux temperature for 3 hours. After chilling, the mixture is acidified with concentrated hydrochloric acid, diluted with water, and extracted twice with methyl chloride. The combined extracts are washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness under reduced presure to furnish 2- or 3-[(cyclohexylmethyl)amino]phenylacetic acid.

EXAMPLES 2-108

Treatment of the indicated halide starting materials set forth in Table I below with ethyl 2- or 3-aminophenyl acetate or methyl 2- or 3-aminobenzoate followed by saponification according to Example 1 is productive of the corresponding 2- or 3-[substituted amino]phenylacetic or benzoic acids listed in Table I.

TABLE I

Example	Starting material	Product
2	1-iodomethyl-2-methyl cyclopentane Chem. Abst. *67*,90421y	2-[(2-methylcyclopentyl)methylamino]phenylacetic acid
3	α-bromomethyl cyclopentane Chem. Abst. *66*, 18472c	3-[(cyclopentyl)methylamino]benzoic acid
4	1-bromomethyl-4-methylcyclohexane Chem. Abst. *70*, 2934b	2-[(4-methylcyclohexyl)methylamino]-phenylacetic acid
5	1-chloromethyl-2-methyl cyclohexane Chem. Abst. *68*, 88671h	3-[(2-methylcyclohexyl)methylamino]-benzoic acid
6	1-(1,2-dimethycyclohexyl)-2-chloropropane Chem. Abst. *73*, 14272j	2-[1-(1,2-dimethylcyclohexyl)-2-propylamino]phenylacetic acid
7	1-(1,3-dimethylcyclohexyl)-2-chloropropane Chem. Abst. *73*, 14272j	3-[1-(1,3-dimethylcyclohexyl)-2-propylamino]benzoic acid
8	1-(1,4-dimethylcyclohexyl)-2-chloropropane Chem. Abst. *73*, 14272j	2-[1-(1,4-dimethylcyclohexyl)-2-propylamino]phenylacetic acid
9	α-bromomethylcycloheptane Chem. Abst. *51*, 1049e	3-(cycloheptylmethylamino)benzoic acid
10	α-bromomethylcyclooctane Chem. Abst. 68,104595t	2-(cyclooctylmethylamino)phenylacetic acid
11	α-chloroethylcyclopentane Chem. Abst. *72*, 110862b	3-(1-cyclopentylethylamino)benzoic acid
12	1-bromo-2-cyclopentylbutane	2-(2-cyclopentylbutylamino)phenylacetic acid
13	1-bromo-2-cyclopentylhexane Ref. A	3-(2-cyclopentylhexylamino)benzoic acid
14	2-chloroethylcyclohexane Chem. Abst. *68*, 86671h	2-(2-cyclohexylethylamino)phenylacetic acid
15	1-(2-bromoethyl)-1-ethycyclohexane Chem. Abst. *70*, 57233c	3-[2-(1-ethylcyclohexyl)ethylamino] phenylacetic acid

16	1-bromo-2-(3-methylcyclohexyl)butane Ref. A	3-[2-(3-methylcyclohexyl)butylamino] phenylacetic acid
17	1-bromo-2-cyclohexylpentane Ref. A.	2-[(2-cyclohexyl)pentylamino]benzoic acid
18	1-bromo-2-cyclohexylbutane Ref. A.	3-[(2-cyclohexyl)butylamino]phenylacetic acid
19	1-bromo-2-cyclohexylpropane Ref. A.	2-[(2-cyclohexyl)propylamino]benzoic acid
20	1-(2-chloroethyl)-2,3-dimethylcyclohexane Chem. Abst. *69*, 56053n	3-[2-(2,3-dimethylcyclohexyl)ethylamino]-phenylacetic acid
21	1-(2-chloroethyl)-3,5-dimethylcyclohexane Chem. Abst. *69*, 56053n	2-[2-(3,5-dimethylcyclohexyl)ethylamino]benzoic acid
22	2-(2-chloroethyl)-1,4-dimethylcyclohexane Chem. Abst. *69*, 56053n	3-[2-(2,5-dimethylcyclohexyl)ethylamino]-phenylacetic acid
23	1-(2-chloroethyl)-2-ethylcyclohexane Chem. Abst. *69*, 56053n	2-[2-(2-ethylcyclohexyl)ethylamino]-benzoic acid
24	1-(2-chloropropyl)-3-methylcyclohexane Chem. Abst. *67*, 53405a	3-[1-(3-methylcyclohexyl)-2-propylamino]-phenylacetic acid
25	1-(2-bromoethyl)-1-methylcyclohexane Chem. Abst. *72*, 132133s	2-[2-(1-methylcyclohexyl)ethylamino]-benzoic acid
26	1-(2-chloroethyl)-2-methylcyclohexane Chem. Abst. *69*, 56053n	3-[2-(2-methylcyclohexyl)ethylamino]-phenylacetic acid
27	1-(2-chloroethyl)-3-methylcyclohexane Chem. Abst. *69*, 56053n	2-[2-(3-methylcyclohexyl)ethylamino]-benzoic acid
28	1-(2-chloroethyl)-4-methylcyclohexane Chem. Abst. *69*, 56053n	3-[2-(4-methylcyclohexyl)ethylamino]-phenylacetic acid
29	2-bromoethylcycloheptane Ref. A.	2-(cycloheptylmethylamino)benzoic acid
30	3-bromopropylcyclobutane Ref. A	3-(3-cyclobutyl)propylamino)phenylacetic acid
31	3-bromopropylcyclopentane Chem. Abst. *75*, 15138f	2-(3-cyclopentyl)propylaminobenzoic acid
32	3-bromopropylcyclohexane Ref. A	3-(3-cyclohexyl)propylamino)phenylacetic acid

33	1-(3-chloropropyl)-3-ethylcyclohexane Chem. Abst. *68*, 12589w	2-[3-(3-ethylcyclohexyl)propylamino]-benzoic acid
34	1-(3-bromopropyl)-3-methylcyclohexane Chem. Abst. *75*,151387f	3-[3-(3-methylcyclohexyl)propylamino]-phenylacetic acid
35	1-(3-bromopropyl)-4-methylcyclohexane Chem. Abst. *75*, 151387f	2-[3-(4-methylcyclohexyl)propylamino]-benzoic acid
36	1-bromo-3-cyclohexyl-pentane Ref. A	3-[(3-cyclohexyl)pentyl-amino]phenylacetic acid
37	(2-bromomethyl)butyl-cyclohexane Ref. A	2-[(3-cyclohexyl-2-ethyl)propylamino]-benzoic acid
38	1-[1-bromo-2-methyl-3-(3-etylcyclohexyl]-propane Chem. Abst. *68*,12529w	3-[3-(3-etylcyclohexyl)-2-methyl]propylaminophenylacetic acid
39	4-bromobutylcyclopentane Chem. Abst. *69*, 18646z	3-(4-cyclopentyl)-butylaminobenzoic acid
40	4-chlorobutylcyclohexane Ref. A	3-(4-cyclohexyl)butyl-aminophenylacetic acid
41	5-bromo-2-cyclohexyl-pentane Ref. A	2-(4-cyclohexyl)pentyl-aminophenylacetic acid
42	1-bromo-4-cyclohexyl-hexane Ref. A Chem. Abst. *70*, P87143r	3-(4-cyclohexyl)hexyl-aminobenzoic acid
43	1-bromo-4-cyclohexyl-2-ethylbutane Ref. A	3-(4-cyclohexyl-2-ethyl)butylaminophenyl acetic acid
44	1-bromo-4-(3-methyl-cyclohexyl)butane Ref. A	2-[4-(3-methylcyclohexyl)butylamino]-benzoic acid
45	1-chloro-4-(4-methyl-cyclohexyl)butane Ref. A	3-[4-(4-methylcyclohexyl)butylamino]-phenylacetic acid
46	1-chloro-4-(4-ethyl-cyclohexyl)butane Ref. A	2-[4-(4-ethylcyclohexyl)butylamino]-benzoic acid
47	1-(4-chlorobutyl)-2,3-dimethylcyclohexane Chem. Abst. *70*, P87143r; Ref. A	3-[4-(2,3-dimethylcyclohexyl)butylamino]phenylacetic acid
48	1-(4-chlorobutyl)-2,5-dimethylcyclohexane Ref. A	2-[4-(2,5-dimethylcyclohexyl)butylamino]benzoic acid

49	1-(4-chlorobutyl)-4-methoxycyclohexane Ref. A	3-[4-(4-methoxylcyclohexyl)butylamino]-phenylacetic acid
50	1-(4-bromobutyl)-2-methoxycyclohexane Ref. A	2-[4-(2-methoxylcyclohexyl)butylamino]-benzoic acid
51	4-bromobutyl)-cycloheptane Ref. A	3-(4-cycloheptyl)butyl-aminophenylacetic acid
52	1-(4-chlorobutyl)-4-cyclohexylcyclohexane Ref. A	2-[4-(4-cyclohexyl)-cyclohexyl]butylamino benzoic acid
53	2-(4-chlorobutyl)-decahydronapthylene Ref. A	3-[4-(2-decahydronaphthyl]butylamino phenylacetic acid
54	4-bromobutylcycloheptane Chem. Abst. *70*, P87143 r	2-(4-cycloheptyl)-butylamino benzoic acid
55	4-chloropentylcyclopropane Chem. Abst. *69*, 105732t, *74*, 31488x	3-[5-(cyclopropyl)-2-pentylamino]phenyl-acetic acid
56	1-bromo-5-cyclobutylpentane Chem. Abst. *70*, P87143r; Ref. A	3-[3-(cyclobutyl)pentyl-amino] benzoic acid
57	1-chloro-5-cyclopentylpentane Chem. Abst. *70*, P87143r; Ref. A	2-[5-(cyclopentyl)-pentylamino]phenyl-acetic acid
58	5-bromopentylcyclohexane Chem. Abst. *55*, 21016e	3-[5-(cyclohexyl)pentyl amino]benzoic acid
59	5-chloropentylcycloheptane Chem. Abst. *70*, P87143r Ref. A	2-[5-(cyclopentyl)pentyl amino]phenylacetic acid
60	6-chlorohexylcyclopentane Ref. A	3-[6-(cyclopentyl)hexyl amino]benzoic acid
61	6-chlorohexylcycloheptane Chem. Abst. *70*, P87143r	2-[6-(cycloheptyl)hexyl amino]phenylacetic acid
62	1-chloro-7-cyclopentylheptane Chem. Abst. *75*, P141605n	3-[7-(cyclopentyl)-heptylamino]benzoic acid
63	8-chlorooctylcyclopentane Ref. A; Chem. Abst. *70*, 87143r	2-[8-(cyclopentyl)-octylaminobenzoic acid
64	8-bromooctylcyclohexane	3-[8-(cyclohexyl)octyl-aminobenzoic acid
65	1-bromo-8-(3,3,5-trimethylcyclohexyl)octane Chem. Abst. *75*, P20026q	2-[8-(3,3,5-trimethyl-cyclohexyl)octylamino]-benzoic acid

66	9-bromononylcyclopentane Ref. A; Chem. Abst. *70*, P87143r	3-[9-(cyclopentyl)-nonylamino]benzoic acid
67	13-bromotridecylcyclo-pentane	2-[13-(cyclopentyl)tri-decylamino]benzoic acid
68	1-(2-chlorocyclopropyl)-pentane Chem. Abst. *75*, 49270a	3-[2-pentyl)cyclo-propylamino]benzoic acid
69	1-bromocyclopropylpentane Chem. Abst. *75*, 76195n	2-[1-pentyl)cyclo-propylamino]benzoic acid
70	1-(2-bromocyclopropyl)-butane Chem. Abst. *74*, 124924b	3-[2-butylcyclopropyl)-amino]phenylacetic acid
71	bromocyclopentane Ref. A	2-cyclopentylamino-benzoic acid
72	1-chloro-1-propylcyclo-pentane Chem. Abst. *52*,	3-(1-propylcyclopentyl-amino)phenylacetic acid
73	4-bromo-1,1-dimethylcyclo-hexane Chem. Abst. *71*, 11242c	2-(4,4-dimethylcyclo-hexylamino)benzoic acid
74	1-chloro-4-propylcyclo-hexane Chem. Abst. *68*, 86671h; *75*, 128994t	3-(4-propylcyclohexyl-amino)phenylacetic acid
75	2-chloro-1-methylethyl-cyclohexane Chem. Abst. *70*, P87143r; *75*, 128994t	2-[2(1-methylethyl)-cyclohexylamino]benzoic acid
76	4-(t-butyl)-1-chloro-1-methylcyclohexane Chem. Abst. *68*, 11389w	3-[4-(t-butyl)-1-methylcyclohexylamino]-phenylacetic acid
77	bromocycloheptane Chem. Abst. *51*, 9505e; *67* 9986s	2-cycloheptylamino-benzoic acid
78	bromocyclooctane Chem. Abst. *51*, 1049e;	3-cycloheptylamino-phenylacetic acid
79	bromocyclononane Chem. Abst. *54*, 4153f; *69*, 2306v	2-cyclononylamino-benzoic acid
80	bromocyclodecane Chem. Abst. *67*, 58849h; *69*, 2306c	3-cyclodecylamino-phenylacetic acid
81	bromocycloundecane	2-cycloundecylamino-benzoic acid
83	bromocyclotridecane Chem. Abst. *69*, 2306c	3-cyclotridecylamino-phenylacetic acid
84	bromocyclotetradecane Chem. Abst. *54*, 4153f; *54*, 16141i	2-cyclotetradecylamino-benzoic acid

85	bromocyclopentadecane Chem. Abst. *72*, P100160g *69*, 2306c	3-cyclopentadecylamino-benzoic acid
86	bromocyclohexadecane Chem. Abst. *69*, 2306c	2-cyclohexadecylamino-phenylacetic acid
87	3-bromobicyclopentyl Chem. Abst. *31*, 7405[3]; *35*, 2864	3-(3-cyclopentyl)cyclo-pentylamino)benzoic acid
88	(3-bromocyclopentyl) cyclohexane Chem. Abst. 31,7405[4]	2-(3-cyclohexylcyclo-pentylamino)phenyl-acetic acid
89	3-bromo-3'-ethybicyclo-pentyl Chem. Abst. *36*, 48089	3-[3-(3-ethylcyclo-pentyl)cyclopentyl-amino]benzoic acid
90	2-bromo-1-cyclopentyl-cyclopentane Chem. Abst. *51*, 5712f	2-[2-(cyclopentyl)-cyclopentylamino]-phenylacetic acid
91	1-chlorobicyclohexyl Chem. Abst. *30*, 3807[1]	3-[1-(cyclohexyl)-cyclohexylamino]-benzoic acid
92	1-chlorobicyclopentyl Chem. Abst. *45*, 6163b	2-[1-(cyclopentyl)-cyclopentylamino]-phenylacetic acid
93	2-iodomethyldecahydro-napthalene Chem. Abst. *41*, 116b	3-[(2-decahydro-naphthyl)methylamino]-benzoic acid
94	2-(2-iodoethyl)deca-hydronaphthalene Chem. Abst. *41*, 116d	2-[2-(2-decahydro-naphthyl)ethylamino]-phenylacetic acid
95	1-(4-bromobutyl)deca-hydronaphthalene Chem. Abst. *45*, p175d	3-[4-(1-decahydro-naphthyl)butylamino]-benzoic acid
96	1-bromo-1,1-dicyclo-pentylethane, Chem. Abst. *31*, 5759[2]	2-[(1,1-dicyclopentyl)-ethylamino]phenyl-acetic acid
97	1-bromo-4-methyldeca-hydronaphthalene Chem. Abst. *53*, 3265f	3-[1-(4-methyldeca-hydronaphthyl)amino] benzoic acid
98	2-(bromomethyl)-1,3,3-trimethylcyclohexane Chem. Abst. 28, 2343[8]	2-[(1,3,3-trimethyl-cyclohexyl)methyl amino]benzoic acid
99	6-(3-bromobutyl)-1,5,5-trimethylcyclohexene Chem. Abst. *66*, 2658g	3-[4-(2,6,6-trimethyl-2-cyclohexenyl)-2-butyl amino]phenylacetic acid
100	4-(3-chloropropyl)-cyclohexane Ref. A	2-[3-(3-cyclohexenyl)-propylamino]benzoic acid

101	3-(4-chlorobutyl)-cyclopentene Ref. A	3-[4-(3-cyclopentenyl)-butylamino]phenylacetic acid
102	1-(4-bromobuty-)cyclo-hexene Chem. Abst. *69*, 76727n	2-[4-(1-cyclohexenyl)-butylamino]benzoic acid
103	1-(5-bromopentyl)-cyclopentene Chem. Abst. *55*, 27129g	3-[5-(1-cyclopentenyl)-pentylamino]phenyl-acetic acid
104	3-(11-chloroundecyl)-cyclopentene Chem. Abst. *37*, 3060f	2-[11-(3-cyclopentenyl)-undecylamino]benzoic acid
105	1-(13-chlorotridecyl-cyclopentene Chem. Abst. *37*, 5031b	3-[13-(1-cyclopentenyl) tridecylamino]phenyl-acetic acid
106	3-(13-chlorotridecyl)-cyclopentene Chem. Abst. *51*, 7652a	2-[13-(3-cyclopentyl) tridecylamino]benzoic acid
107	2-(4-chlorobutyl)deca-hydronapthalene Chem. Abst. *70*, P87143r	3-[4-(2-decahydro-naphthyl)butylamino] phenylacetic acid
108	4-bromo-1-(cyclohexyl)-cyclohexane Chem. Abst. *69*, 103618m	2-[4-cyclohexyl)cyclo-hexylbutylamino]benzoic acid

Ref. A = R.D. Westland, et al., J. Med. Chem., *11*, 1190 (1968)

EXAMPLE 109

Preparation of 2- or 3-[2-(cyclopentyl)ethylamino]phenylacetic acid

To a solution of cyclopentylethan-2-ol (15.0 g) and triethylamine (14 ml) in dry methylene chloride (320 ml.) at -8°C. is added methanesulfonylchloride (5.73 ml.), dropwise. The reaction mixture is stirred at -10°C. for 30 minutes and then diluted with methylene chloride, extracted with ice-water (250 ml.), followed by cold 10% hydrochloric acid (200 ml.); cold saturated sodium bicarbonate (200 ml.) and cold brine (200 ml.). The organic phase is dried over magnesium sulfate and the solvent removed *in vacuo* to provide crude mesylate.

A solution of 18.1 g of the above mesylate and 19.8 g of ethyl 2- or 3-aminophenylacetate in hexamethylphosphoramide is heated at 120°C for 20 hours. After cooling, the reaction mixture is diluted with 30 ml. of ethanol; water (1:1) (30 ml.) and chilled. More ethanol is added and the solid material is collected. This solid is recrystallized twice from ethanol to provide the ester.

A mixture of the ester, 22.0 g, of potassium hydroxide and 200 ml. of ethanol-water (8:1) is stirred under reflux for 6 hours. Concentrated hydrochloric acid (about 80 ml.) is added to the warm mixture and cooling and dilution with water affords a white solid which is collected by filtration and recrystallized from ethanol to yield the product as a white solid.

Treatment of a corresponding 2- or 3-aminobenzoate ester in an analogous manner yields the corresponding N-alkylatedaminobenzoic acid.

EXAMPLES 110-185

Treatment of the alcohols of Table II below with methanesulfonylchloride to provide the corresponding mesylate followed by treatment with ethyl 2- or 3-aminophenylacetate or methyl 2- or 3-aminobenzoate followed by saponification and acidification of the resulting substituted 2- or 3-aminophenylacetate or 2- or 3-aminobenzoate by the procedures of Example 109 produces the indicated 2- or 3-(substituted-amino)phenylacetic or benzoic acids shown in Table II.

TABLE II

Example	Starting Material	Product.
110	2-isopropyl-5-methyl-enecyclopentanol Chem. Abst. *66*, 38074c	2-(2-isopropyl-5-methyl enecyclopentylamino-phenylacetic acid
111	2-cyclohexen-1-ol Aldrich Chem. Co.	3-(cyclohex-2-enylamino)-benzoic acid
112	4-isopropyl-2-cyclo-hexen-1-ol Chem. Abst. *69*, 99290d	2-(4-isopropylcyclo-hex-2-enylamino)benzoic acid
113	2-isopropyl-3-cyclo-hexen-1-ol Chem. Abst. *75*, 55380m	3-(2-isopropylcyclox-hex-3-enylamino)phenyl acetic acid
114	2-(2-(cylopentyl)cyclo-1-olopentane Chem. Abst. *69*, 27127h	2-)2-(cylopentyl)cyclo-pentylamino)benzoic acid
115	2-cyclononen-1-ol Chem. Abst. *72*, 30882t	3-(cyclonon-2-enylamino)-phenylacetic acid
116	3-cyclononen-1-ol Chem. Abst. *75*, 13957j	2-(cyclonon-3-enylamino)-benzoic acid
117	2-methylenecyclo-decanol Chem. Abst. *74*, 75857w	3-(2-methylenecyclodecyl-amino)phenylacetic acid
118	E-3-cyclodecen-1-ol Chem. Abst. *73*, 87173n	2-(E-cyclodec-3-enyl-amino)benzoic acid
119	Z-3-cyclodecen-1-ol Chem. Abst. *73*, 87173n	3-(Z-cyclodec-3-enyl amino)phenylacetic acid
120	5-cyclodecen-1-ol Chem. Abst. *71*, 60514w	2-(cyclodec-5-enyl-amino)benzoic acid
121	4-ethyl-2-cyclododecen-1-ol Chem. Abst. *70*, 114922c	3-(4-ethylcyclododec-2-enylamino)phenylacetic acid
122	2-cyclotridecen-1-ol Chem. Abst. *70*, 114922c	2-(cyclotridec-2-enyl-amino)benzoic acid
123	8-cycloheptadecen-1-ol Chem. Abst. *66*, 2658g	3-(cycloheptadec-8-enyl-amino)phenylacetic acid
124	9-cycloheptadecen-1-ol Chem. Abst. *68*, 49157z	2-(cycloheptadec-9-enyl-amino)benzoic acid
125	2-cyclobutene-1-methanol Chem. Abst. *67*,32343p	3-[(cyclobut-2-enyl)meth-ylamino]phenylacetic acid

126	1-cyclobutene-1-methanol Chem. Abst. *71*, 12650 r	2-[(cyclobut-1-enyl)-ethylamino]benzoic acid
127	2-cyclopentene-1-methanol Chem. Abst. *71*, 12650r	2-[(cyclopent-3-enyl)-methylamino]phenylacetic acid
128	3-cyclopentene-1-methanol Chem. Abst. *73*, 65783j	3-(4-isopropylcyclohex-2-enylamino]benzoic acid
129	1-cyclopenten-1-propanol Chem. Abst. *73*, 66113c	2-[1-(cyclopent-1-enyl)-propylamino]phenylacetic acid
130	1-cyclohexene-1-methanol Chem. Abst. *70*, 10773p	3-[(cyclohex-1-enyl)-methylamino]benzoic acid
131	2-cyclohexene-1-ethanol, 30882t Chem. Abst. *69*, 26424r	2-[(1-cyclohex-2-enyl)-ethylamino]phenylacetic acid
132	1-(3-cyclohexenyl)-1-propanol Chem. Abst. *67*, 72634r	3-[(1-cyclohex-3-enyl)-propylamino]benzoic acid
133	*cis*-5-ethyl-3-cyclo-hexene-1-methanol Chem. Abst. *69*, 27575c	2-(*cis*-5-ethylcyclohex-3-enyl)methylaminophenyl-acetic acid
134	*trans*-5-ethyl-3-cyclo hexene-1-methanol Chem. Abst. *69*, 27575c	3-(*trans*-5-ethylcyclohex-3-enyl)methylaminobenzoic acid
135	1-cycloheptene-1-methanol Chem. Abst. *73*, 14266k	2-(cyclohept-1-enylmethyl-amino)phenylacetic acid
136	1-cycloheptene-1-ethanol Chem. Abst. *70*, 37270j	3-[1-(cyclohept-1-enyl)-ethylamino)benzoic acid
137	2-cyclooctene-1-methanol Chem. Abst. *69*, 36263b	2-(cyclooct-2-enyl-methylamino)phenyl acetic acid
138	4-cyclooctene-1-methanol Chem. Abst. *66*, 37492a	3-(cyclooct-4-enylmethyl-amino)benzoic acid
139	1-cyclooctenylethanol Chem. Abst. *70*, 37270j	2-(cyclooct-1-enylethyl-amino)phenylacetic acid
140	2-(3-cyclopentenyl) butanol Chem. Abst. *72*, 133044a	2-[2-ethyl-2-cyclopent-3-enylethylamino]benzoic acid
141	2,3-dimethyl-2-(2-cyclopentenyl)propanol Chem. Abst. *70*, 11818u	3-[2-(2,3-dimethylcyclopent-2-enyl)propylamino]-phenylacetic acid

142	4,6-dimethyl-3-cyclohexen-1-ethanol Chem. Abst. 111623c	2-[2-(4,6-dimethylcyclohex-3-enyl)ethylamino]-benzoic acid
143	α-methyl-1-cyclohexene-1-ethanol Chem. Abst. *74*, 42909v	3-[1-methyl-2-(cyclohex-1-enyl)ethylamino]phenylacetic acid
144	4-methyl-3-cyclohexene-1-ethanol Chem. Abst. *75*, 19601s	2-[2-(4-methylcyclohex-3-enyl)ethylamino]benzoic acid
145	1-cyclooctene-1-ethanol Chem. Abst. *70*, 37270j	3-(2-cyclooct-1-enylethylamino)phenylacetic acid
146	1-cyclononene-1 ethanol	2-(2-cyclonon-1-enylethylamino)benzoic acid
147	α,4-dimethyl-3-cyclohexene-1-propanol Chem. Abst. *68*, 78427t	3-[1-methyl-3-(4-methylcyclohex-3-enyl)propylamino]phenylacetic acid
148	1-cyclohexene-1-propanol Chem. Abst. *70*, 87111d	2-(3-cyclohex-1-enylpropylamino)benzoic acid
149	3-cyclohexene-1-propanol Chem. Abst. *69*, 43158z	3-(3-cyclohex-3-enylpropylamino)phenylacetic acid
150	3-cyclohexene-1-butanol Chem. Abst. *69*, 49158z	2-(4-cyclohex-3-enylbutylamino)benzoic acid
151	, -dimethyl-2-cyclopentene-1-undecanol Chem. Abst. *72*, 110860z	3-[(1,1-dimethyl-11-cyclopent-2-enyl)undecylamino]-phenylacetic acid
152	4-isopropylidene 2,2-dimethylcyclobutanol Chem. Abst. *73*, 24996n	2-(2,2-dimethyl-4-isopropylidenecylobutylamino)benzoic acid
153	2-cyclopenten-1-ol Chem. Abst. *68*, 39177s	2-(cyclopent-2-enylamino)-phenylacetic acid
154	3-cyclopenten-1-ol Chem. Abst. *66*, 11504r	3-(cylopent-3-enylamino)-benzoic acid
155	3-cyclohexen-1-ol Chem. Abst. *69*, 26837c	2-(cyclohex-3-enylamino)-phenylacetic acid
156	2,2-dimethyl-6-methylenecyclohexanol	3-(2,2-dimethyl-6-enylcyclohexylamino)benzoic acid
157	2-methylenecycloheptanol Chem. Abst. *69*, 27127h	2-(2-methylenecycloheptylamino)phenylacetic acid
158	2-methyl-2-cyclohepten-1-ol Chem. Abst. *69*, 27127h	3-(2-methylcyclohept-2-enylamino)benzoic acid

159	2-methyl-6-methylene-cycloheptanol Chem. Abst. *67*, 11600e	2-(2-methyl-6-methyl-enylcycloheptylamino)-phenylacetic acid
160	3,7-dimethyl-3-cyclo-hepten-1-ol Chem. Abst. *67*, 11600e	3-(3,7-dimethylcyclohept-3-enylamino)benzoic acid
161	4-cycloocten-1-ol Chem. Abst. *70*, 28287t	2-(cyclooct-4-enylamino) phenylacetic acid
162	3-cycloocten-1-ol Chem. Abst. *66*, 104593z	3-(cyclooct-3-enylamino)-benzoic acid
163	2-cycloocten-1-ol Chem. Abst. *68*, 39177s	2-(cyclooct-2-enylamino)-phenylacetic acid
164	4-methylenecyclo-octanol Chem. Abst. *70*, 28445t	3-(4-methylenecyclo-octylamino)benzoic acid
165	α-methyl-5-methylene-cyclooctanemethanol Chem. Abst. *68*, 104595t	2-[1-(5-methylenecyclo-octylethylamino]phenyl-acetic acid
166	5-methylenecyclo-octanemethanol Chem. Abst. *66*, 37492a	3-[5-methylenecyclo-octylmethylamino]-benzoic acid
167	1,3-dimethyl-2-methyl-enecyclopentane-methanol Chem. Abst. *73*, 24996n	2-[(1,3-dimethyl-2-methylenecyclopentyl)-methylaminobenzoic acid
168	E-4-cyclopropyl-3-buten-2-ol	3-[*E*-2-(4-cyclopropyl)-but-3-enylamino]phenyl-acetic acid
169	Z-4-cyclopropyl-3-buten-2-ol anol Chem. Abst. *70*, 3413t	2-[*Z*-2-(4-cyclopropyl)-but-3-enylamino]benzoic acid
170	α-methylenecyclo-hexaneethanol Chem. Abst. *66*, 45950p	3-[(1-methylene-2-cyclohexyl)ethyl-amino]phenylacetic acid
171	β-methylenecyclo-hexaneethanol Chem. Abst. *75*, 139951c	2-[(2-methylene-2-cyclo-hexyl)ethylamino]-benzoic acid
172	*E*-2-)3,3-dimethylcyclo-hexylidenyl)ethanol Chem. Abst. *75*, 110431x	3-(*E*-2-(3,3-dimethyl-cyclohexylidenyl)ethyl]-aminophenylacetic acid
173	*Z*-2-(3,3-dimethylcyclo-hexylidenyl)ethanol Chem. Abst. *75*, 110431x	2-(*Z*-2-(3,3-dimethyl-cyclohexylidenylethyl-amino]benzoic acid
174	*E*-4-cyclopentyl-2-buten-1-ol Chem. Abst. *75*, 48349w	3-(4-cyclopentylbut-2-enylamino]phenylacetic acid

175	*E*-4-cyclohexyl-2-buten-1-ol Chem. Abst. *75*, 48349w	2-[*E*-4-cyclohexylbut-2-enylamino]benzoic acid
176	2-vinylcyclopentane-ethanol Chem. Abst. *66*, 104477q	3-[2-(2-vinylcyclo-pentyl)ethylamino] phenylacetic acid
177	3-isopropyl-1-methyl-cyclopentanemethanol Chem. Abst. *66*, 38061w	2-[(3-isopropyl-2-methylcyclopentyl)-methylamino]benzoic acid
178	1-allyl-2-methylcyclo-hexanol Chem. Abst. *71*, 29919h	3-(1-allyl-2-methyl-cyclohexylamino)phenyl-acetic acid
179	2-isopropenylcyclo-hexanol Chem. Abst. *72*, 12663t	2-(2-isopropenylcyclo-hexylamino)phenylacetic acid
180	1-(isopropenylcyclo-hexanol Chem. abst, *75*, 139951c	3-(1-isopropenylcyclo-hexylamino)benzoic acid
181	2-allylcyclohexanol Chem. Abst. *70*, 96517t	2-(2-allylcyclohexyl-amino)phenylacetic acid
182	3-allylcyclohexanol Chem. Abst. *69*, 86453j	3-(3-allylcyclohexyl-amino)benzoic acid
183	1-allylcyclohexanol Chem. Abst. *66*, 374866	2-(1-allylcyclohexyl-amino)phenylacetic acid
184	1-(3-butenyl)-2-methyl cycloheptanol Chem. Abst. *69*, 106892g	3-[1-(3-butenyl)-2-methylcycloheptylamino] benzoic acid
185	1-allylcyclododecanol Chem. Abst. *68*, 95381r	2-(1-allylcyclododecyl-amino)phenylacetic acid
186	2-butyl-2-cyclopenten-1-ol Chem. Abst. *71*, 38404p	3-(2-butylcyclopent-2-en-ylamino)benzoic acid

EXAMPLE 187

Preparation of Esters

Treatment of the acids of Examples 1-186 with trifluoroacetic anhydride to provide the N-$COCF_3$ derivatives, followed by treatment with thionyl chloride to provide the N-$COCF_3$ acid chloride, followed by treatment with one of the following alcohols, followed by removal of the N-$COCF_3$ group with sodium hydroxide, provides the corresponding esters of the starting acid.

Alcohols: methanol, ethanol, 2-methoxyethanol, butanol, pentanol, hexanol cyclopentanol, cyclohexanol, 1,2-propanediol, 1,3-propanediol, ethylene glycol, glycerol, glycidol, glycolic acid, citric acid, tartaric acid, malic acid, methyl glycolate, 2-hydroxypropionic acid, 3-hydroxybutyhric acid 4-hydroxybutyric acid, glyceric acid, 3-diethylamino-1-propanol, 1-diethylamino-2-propanol, 1-dimethylamino-2-propanol, 3-dimethylamino-1-propanol, 2-diisopropylamino-ethanol, 3-diethylamino-1,2-propanediol, *N*-piperideneethanol, N,N-diethylethanolamine, benzyl alcohol, p-fluorobenzyl alcohol, *p*-bromobenzyl alcohol, *p*-chlorobenzyl alcohol, *p*-methoxybenzyl alcohol, *m*-chlorobenzyl alcohol, *m*-(trifluoromethyl)benzyl alcohol, *p*-carboxybenzyl alcohol, phenol *p*-fluorophenol, *p*-bromophenol, *p*-chlorophenol, *p*-methoxyphenol, *p*-carboxyphenol, *m*-(trifluoromethyl)phenol, 4-cyanophenol, 3-hydroxypyridine, 2-chloro-3-hydroxy-pyridine, and 5-carboxy-3-hydroxypyridine.

EXAMPLE 188

Preparation of 2-[(cyclohexyl)methylamino]hydrocinnamic acid

A 4 g. sample of ethyl 2-[(cyclohexyl)methylamino]-hydrocinnamate is hydrolyzed with 1.6 g. 85% potassium hydroxide in 60 ml. 95% ethanol by refluxing the solution for 5 hours. The solution is cooled,

diluted with 100 ml. water and acidified to pH 4.5 with 37% hydrochloric acid. The precipitate is collected, dried *in vacuo* and crystallized from acetone to yield the title compound as white powder.

EXAMPLE 189

Preparation of 1-methanesulfonyloxy-2-allylcyclohexane

To a mixture of 250 ml. of dichloromethane, 25 g. 2-allycyclohexanol and 16.7 g. of triethylamine cooled in an ice-salt bath to -10°C. is added dropwise, over 15 minutes, 18.9 g. of methanesulfonyl chloride. The mixture is cooled at -10°C. to -15°C. for 30 minutes and then washed with 300 ml. each of cold water, 10% hydrochloric acid, sodium carbonate solution and with saturated sodium chloride solution. The organic layer is dried with magnesium sulfate and concentrated *in vacuo* to give a pale yellow oil.

EXAMPLE 190

Preparation of ethyl 3-[(2-methylcyclopentyl)methylamino]phenylacetate

To a cold (-20°) stirred solution of 10.8 g. 1-hydroxymethyl-2-methylcyclopentane prepared by lithium aluminum hydride reduction of methyl 2-methylcyclopentanecarboxylate and 13.4 ml. triethylamine in 300 ml. ether is added dropwise 5.6 ml. methanesulfonyl chloride in 5 ml. of either. After addition is completed, the solution is warmed to room temperature, stirred for 30 minutes and filtered directly into a solution of 23.1 g. ethyl 3-aminophenyl acetate in 100 ml. ether. After 17 hours at room temperature, the precipitate is filtered and washed with several portions of methylene chloride. The organic solution is washed twice with 100 ml. water, 100 ml. brine, dried and evaporated. The tan residue is crystallized from ethanol and from acetonitrile to yield the title compound as white crystals.

EXAMPLE 191

Preparation of ethyl 2-[(3-isopropyl-2-methylcyclopentyl)methylamino]hydrocinnamate

A solution of 8.6 ethyl 2-aminohydrocinnamate, 9.77 g. 3-isopropyl-2-methylcyclopentanecarboxaldehyde and a few crystals of 2,4-dinitrobenzenesulfonic acid in 250 ml. toluene is refluxed under a Dean-Stark trap for 17 hours, whereupon the theoretical amount (0.8 ml.) water has been collected. The toluene is evaporated to yield ether 3-[2-(3-isopropyl-2-methylcyclopentyl)methyleneamino)phenyl]propionate as a crystalline mass.

To a mixture of 17.8 g. of the above compound in 250 ml. ethanol is added 1.68 g. sodium borohydride and the mixture is stirred at room temperature for 18 hours. Excess reagent is decomposed by addition of 10 ml. acetic acid. The solution is concentrated *in vacuo* and the residue is partitioned between toluene and aqueous potassium carbonate. After drying, the toluene is evaporated to yield a solid. Crystallization from acetonitrile and from ethanol affords the title compound as white crystals.

EXAMPLE 192

Preparation of ethyl 3-[3-(2-allylcyclohexylamino)phenyl]propionate

A mixture of 5.0 g. of ethyl 3-aminohydrocinnamate, 10.0 g. of 1-methanesulfonyloxy-2-allylcyclohexane (prepared by the method of Example 189), 4.2 g. of anhydrous powdered potassium carbonate and 40 ml. hexamethylphosphoramide is heated to 80°C for 17 hours. The mixture is then cooled, diluted with water and extracted with ethyl ether. The ether extracts are washed with water, dried and evaporated. The residue is recrystallized from ethanol yielding the title compound as white crystals.

EXAMPLE 193

Preparation of ethyl 2-[(4-cycloheptyl)butylamino]cinnamate

A mixture of ethyl 2-aminocinnamate, 5.9 g. 4-bromobutylcycloheptane and one equivalent of anhydrous powdered potassium carbonate in 50 ml. hexamethylphosphoramide is heated for 20 hours at 60°C. The mixture is then cooled, diluted with water and extracted with ether. The combined ether extracts are dried, filtered and evaporated. Crystallization from acetonitrile provides the title compound as white crystals.

TABLE III

The following 2- or 3-[(cycloalkylor cycloalkenyl substituted)amino, alkylamino or alkenylamino]hydrocinnamates are prepared from the appropriate starting material by the method shown. Alcohols are converted to the corresponding mesylate by the method of Example 189.

Example No.	Method of Example	2- or 3-(Substituted-amino)hydrocinnamate
194	190	Ethyl 2-[(cyclopentyl)methylamino]-hydrocinnamate
195	193	Ethyl 3-[1-(1,4-dimethylcyclohexyl)-2-propylamino]hydrocinnamate
196	191	Ethyl 2-(2-cyclopentylbutylamino)-hydrocinnamate
197	192	Ethyl 3-(4-cyclopentylbutylamino)-hydrocinnamate
198	193	Ethyl 2-cyclodecylaminohydrocinnamate
199	190	Ethyl 3-(3-cyclohexylcyclopentylamino) hydrocinnamate
200	192	Ethyl 2-[2-(2-decahydronaphthyl)-ethylamino]hydrocinnamate
201	190	Ethyl 3-(2-isopropyl-5-methylene-cyclopentylamino)hydrocinnamate
202	193	Ethyl 2-(4-isopropylcyclohex-2-enyl-amino)hyrocinnamate
203	190	Ethyl 3-[2-(2,3-dimethylcyclopent-2-enyl)propylamino]hydrocinnamate
204	192	Ethyl 2-(cyclopent-2-enylamino)-hydrocinnamate
205	192	Ethyl 3-(1-allylcyclododecylamino)-hydrocinnamate

TABLE IV

The following 2- or 3-[(cycloalkyl or cycloalkenyl substituted)amino, alkylamino or alkenylamino]hydrocinnamic acids are prepared from the esters of Table III by the method of Example 188.

Example No.	2- or 3-(Substituted-amino)hydrocinnamic acids
206	2-[(Cyclopentyl)methylamino]hydrocinnamic acid
207	3-[1-(1,4-Dimethylcyclohexyl)-2-propylamino]-hydrocinnamic acid
208	2-(2-Cyclopentylbutylamino)hydrocinnamic acid
209	3-(4-Cyclopentylbutylamino)hydrocinnamic acid
210	2-Cyclodecylaminohydrocinnamic acid
211	3-(3-Cyclohexylcyclopentylamino)hydrocinnamic acid
212	2-[2-(2-Decahydronaphthyl)ethylamino]hydrocinnamic acid
213	3-(2-Isopropyl-5-methylenecyclopentylamino)-hydrocinnamic acid
214	2-(4-Isopropylcyclohex-2-enylamino)hydrocinnamic acid
215	3-[2-(2,3-Dimethylcyclopent-2-enyl)propylamino]-hydrocinnamic acid
216	2-(Cyclopent-2-enylamino)hydrocinnamic acid
217	3-(1-Allylcyclododecylamino)hydrocinnamic acid

TABLE V

The following 2- or 3-[(Cycloalkyl or cycloalkenyl substituted) amino, alkylamino or alkenylamino] cinnamates are prepared from the appropriate starting materials by the methods shown. Alcohols are converted to their corresponding mesylate by the method of Example 189.

Example No.	Method of Example	2- or 3-(Substituted-amino)cinnamate
218	190	Ethyl 2-[(cyclopentyl)methlamino]-cinnamate
219	193	Ethyl 3-[(4-methylcyclohexyl)methyl-amino]cinnamate
220	192	Ethyl 2-[1-(1,4-dimethylcyclohexyl)-2-propylamino]cinnamate
221	192	Ethyl 3-[2-(2-methylcyclohexyl)ethyl-amino]cinnamate
222	193	Ethyl 2-[3-(3-ethylcyclohexyl)-2-methyl]propylaminocinnamate
223	192	Ethyl 3-[5-(cyclopropyl)-2-pentyl-amino]cinnamate
224	191	Ethyl 2-(3-cyclohexylcyclopentyl-amino)cinnamate
225	190	Ethyl 3-[4-(1-decahydronaphthyl)butyl-amino]cinnamate
226	193	Ethyl 2-(cyclonon-2-enylamino)cinnamate
227	190	Ethyl 3-[(1-cyclohex-2-enyl-)ethyl-amino]cinnamate
228	192	Ethyl 2-[1-methyl-2-(cyclohex-1-enyl)-ethylamino]cinnamate
229	193	Ethyl 3-[(2-methylene-2-cyclohexyl-ethyl)amino]cinnamate
230	192	Ethyl 2-(1-isopropenylcyclohexylamino) cinnamate

TABLE VI

The following 2- or 3-[cycloalkyl or cycloalkenyl substituted)amino, alkylamino or alkenyl amino]cinnamic acids are prepared from the esters of Table V by the method of Example 188.

Example No.	2- or 3-(Substituted-amino)cinnamic acid
231	2-[(Cyclopentyl)methylamino]cinnamic acid
232	3-[(4-Methycyclohexyl)methylamino]cinnamic acid
233	2-[1-(1,4-Dimethylcyclohexyl)-2-propylamino]-cinnamic acid
234	3-[2-(2-Methylcyclohexyl)ethylamino]cinnamic acid
235	2-[3-(3-Ethylcyclohexyl)-2-methylpropylamino]-cinnamic acid
236	3-[5-(Cyclopropyl)-2-pentylamino]cinnamic acid
237	2-(3-Cyclohexylcyclopentylamino)cinnamic acid
238	3-[4-(1-Decahydronaphthyl)butylamino]cinnamic acid
239	2-(Cyclonon-2-enylamino)cinnamic acid
240	3-[(1-Cyclohex-2-enyl)ethylamino]cinnamic acid
241	2-[1-Methyl-2-(cyclohex-1-enyl)ethylamino]-cinnamic acid
242	3-[(2-Methylene-2-cyclohexylethyl)amino]-cinnamic acid
243	2-(1-Isopropenylcyclohexylamino)cinnamic acid

TABLE VII

The following 2- or 3-[(cycloalkyl or cycloalkenyl substituted)amino, alkylamino or alkenylamino]phenylpropiolates are prepared from the appropriate starting materials by the methods shown. Alcohols are converted to their corresponding mesylate by the method of Example 189.

Example No.	Method of Example	2- or 3-(Substituted-amino)phenylpropiolate esters
244	191	Ethyl 2-[(cyclopentyl)methylamino]-phenylpropiolate
245	193	Ethyl 3-(2-cyclopentylbutylamino)-phenylpropiolate
246	193	Ethyl 2-(4-cycolopentyl)-butylamino-phenylpropiolate
247	192	Ethyl 3-[2-(2-decahydronaphthyl)ethyl-amino]phenylpropiolate
248	192	Ethyl 2-(4-isopropylcyclohex-2-enyl-amino)phenylpropiolate
249	190	Ethyl 3-(cyclopent-2-enylamino)phenyl-propiolate
250	190	Ethyl 2-(1-allylcyclododecylamino)-phenylpropiolate

TABLE VIII

The following 2- or 3-[cycloalkyl or cycloalkenyl substituted)amino, alkylamino, or alkenylamino]phenylpropiolic acids are prepared from the esters of Table VII by the method of Example 188.

Example No.	2- or 3-(Substituted-amino)phenylpropiolic acid
251	2-[(Cyclopentyl)methylamino]phenylpropiolic acid
252	3-(2-Cyclopentylbutylamino)phenylpropiolic acid
253	2-(4-Cyclopentylbutylamino)phenylpropiolic acid
Example No.	2- or 3-(Substituted-amino)phenylproiolic acid
254	3-[2-(2-Decahydronaphthyl)ethylamino]phenyl-propiolic acid
255	2-(4-Isopropylcyclohex-2-enylamino)phenyl-propiolic acid
256	3-(Cyclopent-2-enylamino)phenylpropiolic acid
257	2-(1-Allylcyclododecylamino)phenylpropiolic acid

TABLE IX

The following 2- or 3-[(cycloalkyl or cycloalkenyl substituted)amino, alkylamino or alkenylamino]phenylbutyrates are prepared from the appropriate mesylates by the method of Example 192. The requisite mesylates are prepared by the method of Example 189

Example No.	2- or 3-(Substituted-amino)phenylbutyrate esters
258	Ethyl 4-[2-(2-butylcyclopent-2-enylamino)-phenyl]butyrate
259	Ethyl 4-[3-(1-allylcyclohexylamino)phenyl]-butyrate
260	Ethyl 4-[2-(cyclooct-2-enylamino)phenyl]-butyrate
261	Ethyl 4-[3-(cycloheptyl)butylamino]phenyl-butyrate
262	Ethyl 4-[2-(1-cyclopentylethylamino)phenyl]-butyrate
263	Ethyl 4-[3-(cyclooctylmethylamino)phenyl]-butyrate

TABLE X

The following 2- or 3-[cycloalkyl or cycloalkenyl substituted amino, alkylamino or alkenylamino]phenylbutyric acids are prepared from the esters of Table IX by the method of Example 188.

Example No.	2- or 3-(Substituted-amino)phenylbutyric acid
264	4-[2-(2-Butylcyclopent-2-enylamino)phenyl]-butyric acid

Example No.	2- or 3-(Substituted-amino)phenylbutyric acid
265	4-[3-(1-Allylcyclohexylamino)phenyl]butyric acid
266	4-[2-(Cyclooct-2-enylamino)phenyl]butyric acid
267	4-[3-(Cycloheptyl)butylamino]phenylbutyric acid
268	4-[2-(1-Cyclopentylethylamino)phenyl]butyric acid
269	4-[3-(Cyclooctylmethylamino)phenyl]butyric acid

EXAMPLE 270

Preparation of 2-(2-allylcyclohexylamino)acetophenone

2-Aminoacetophenone is heated with 5 g. 1-methanesulfonyloxy-2-allylcyclohexane (prepared by the method of Example 189) in 50 ml. hexamethylphosphoramide containing anhydrous potassium carbonate (1.9 g.) for 16 hours a 100°C. The solution is cooled to room temperature, filtered to remove solids, and the filtrate is diluted with cold water (50 ml.). The amber solid so obtained is collected and washed with water. Recrystallization from ethanol followed by dichloromethane provides 2-(2-allylcyclohexylamino)acetophenone.

Treatment of the corresponding 3-substituted acetophenone in an analogous manner yields the correspondingly substituted 3-acetophenone.

TABLE XI

The following 2- or 3-[(cycloalkyl or cycloalkenyl substituted)amino, alkylamino or alkenylamino]acetophenones are prepared by the method of Example 270. The requisiste mesylates are prepared by the method of Example 189.

Example No.	2- or 3-(Substituted-amino)acetophenone
271	2-(2-Butylcyclopent-2-enylamino)acetophenone
272	3-[(1-Cyclohex-2-enyl)ethylamino]acetophenone
273	2-(Cycloheptadec-8-enylamino)acetophenone
274	3-(2-Cyclohexylethylamino)acetophenone
275	2-[(Cyclopentyl)methylamino]acetophenone

EXAMPLE 276

Preparation of sodium 2-(1-cyclopentylethylamino)phenylacetate

A mixture of 3.62 g. of 2-(1-cyclopentylethylamino)phenylacetic acid and 25 ml. of ethanol water (9:1) containing 0.400 g. of sodium hydroxide is stirred for 4 hours. The mixture is filtered and the residue washed with 10 ml. of ethanol-water (9:1) and dried *in vacuo* for 24 hours to yield sodium 2-(1-cyclopentylethylamino)phenyl acetate as a white solid.

Treatment of a corresponding 2- or 3-substituted benzoic acid in an analogous manner yields the corresponding 2- or 3- substituted sodium benzoate.

EXAMPLE 277

Preparation of 2- or 3-(2-cyclopentylbutylamino)phenylacetyl chloride

A cold solution of 25 g. 2- or 3-(2-cyclopentylbutylamino)phenylacetic acid in 500 ml. dimethoxyethanemethylene chloride (4:1) is prepared and dry hydrochloric acid is bubbled through the solution until no more precipitate forms. The solution is treated with 25 ml. thionyl chloride and refluxed until all of the precipitate has dissolved. The solvents are evaporated to yield the acid chloride hydrochloride as an orange, semi-crystalline mass.

Treatment of a 2- or 3-substituted benzoic acid in an analogous manner yields the corresponding 2- or 3-substituted benzoyl chloride.

EXAMPLE 278

Preparation of 2- or 3-(N-trifluoroacetyl-l-cyclopentylethyl-amino)phenylacetyl chloride

A stirred ice-cold suspension of 9 g. 2- or 3-(1-cyclopentylethylamino)phenylacetic acid in 100 ml. of dimethoxyethane and 161. of pyridine is treated with 18 ml. of trifluoroacetic anhydride at 0°C. The solution is stirred for 30 minutes at room temperature and then diluted with 300 ml. ether and 100 g. ice. After stirring vigorously for 15 minutes, the phases are separated, the ether solution is washed with brine, dried and evaporated to a white, amorphous solid.

To a solution of 9.2 g. of the above solid in 30 ml. methylene chloride and 0.5 ml. of dimethylformamide is added 5.7 ml. thionyl chloride. After 20 hours at reflux, the solvents are evaporated to yield 2- or 3-[N-trifluoroacetyl-1cyclopentylethylamino)phenylacetyl chloride as a light yellow, mobile oil.

EXAMPLE 279

Preparation of 2- or 3-(N-carbobenzyloxy-N-cyclooctylmethylamino)benzoyl chloride

To 15 g. 2- or 3-(cyclooctylmethylamino)benzoic acid in 200 ml. warm chloroform is added a solution of 12 g. sodium carbonate in 150 ml. water. To the vigorously stirred solution is added 10 g. carbobenzyloxy chloride. After 2 hours stirring at 40°C., the layers are separated, washed three times with 1*N* hydrochloric

acid, dried, and evaorated to an oil. The oil is dissolved in 30 ml. methylene chloride and evaorated to an oil. The oil is dissolved in 300 ml. toluene, treated with 15 ml. thionyl chloride and the solution is refluxed for 5 hours. The solvents are evaporated and the residue is dissolved three times in toluene, evaporating each time ultimately to yield 2- or 3-(N-carbobenzyloxycyclooctylmethylamino)benzoyl chloride as a viscous, orange oil.

EXAMPLE 280

Preparation of 1-[2- or 3-(N-tert-butyloxycarbonyl)cyclopentylethylaminophenylacetyl]imidazole

To a solution of 10 g. 2- or 3-(cyclopentylethylamino)phenylacetic acid in 100 ml. dioxane is treated with 4.0 g. *tert*-butylazidoformate and 10 ml. pyridine. After stirring at room temperature for 18 hours, the protected amidoacid is precipitated from solution by the addition of 150 ml. water. The solid is collected, thoroughly dried, and dissolved in 200 ml. of a mixture consisting of methylene chloride/dimethoxyethane/ pyridine (1:4:1). To this solution is stirred overnight at room temperature and the solvents are evaporated to yield 1-[2- or 3-(N-*tert*-butyloxycarbonyl)cyclopentylethylaminophenylacetyl]imidazole as an orange oil.

EXAMPLE 281

Preparation of diethyl 2- or 3-(1-cyclopentylethylamino)benzoylmalonate

A solution of 26.6 g. of diethyl malonate and 10 ml. of 1, 2-dimethoxyethane is added to a suspension of 4.0 g. of 2- or 3-(1-cyclopentylethylamino)benzoyl chloride hydrochloride in 1,2-dimethoxyethane under argon. A solution of 17.3 g. of 1,2-dimethoxyethane is then added. The reaction mixture is refluxed for 4.5 hours, cooled, poured on ice, acidified, and extracted with ether. The ether solution is washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated to dryness. Addition of a small amount of ethanol to the residue gives a solid which is filtered and discarded. The ethanol filtrate is concentrated and the residue is crystallized from ether to yield diethyl 2- or 3-(1-cyclopentylethylamino)benzoylmalonate.

EXAMPLE 282

Preparation of tert-butyl ethyl 2- or 3-(1-cyclopentylethylamino)benzoylmalonate

A solution of 28.0 g. of *tert*-butyl ethyl malonate in 10 ml. of 1,2-dimethoxyethane is added to a suspension of 4.0 g. of sodium hydride in 1,2-dimethoxyethane under argon. A solution of 17.3 g. of 2- or 3-(1-cyclopentylethylamino)benzoyl chloride hydrochloride in 1.2-dimethoxyethane is then added. The reaction mixture is refluxed for 5 hours, cooled, poured on ice and extracted with ether. The ether solution is washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated to dryness. The residue is then recrystallized from ether to yield *tert*-butyl ethyl 2- or 3-(1-cyclopentylethylamino)benzoyl malonate.

EXAMPLE 283

Preparation of ethyl 2-[2- or 3-(1-cyclopentylethylamino)benzoylacetoacetate

A solution of 21.6 g. of ethyl acetoacetate and 10 ml. of 1,2-dimethoxyethane is added to a suspension of 4.0 g. of sodium hydride in 1,2-dimethoxyethane under argon. A solution of 17.3 g. of 2-or 3-(1-cyclopentylethylamino)benzoyl chloride hydrochloride in 1,2-dimethoxyethane is then added. The reaction mixture is refluxed for 5 hours, cooled, poured on ice and extracted with ether. The ether solution is washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated to dryness. Recrystallization from ether affords ethyl 2-[2- or 3-(1-cyclopentylethylamino)benzoyl]acetoacetate as a while solid.

EXAMPLE 284

Preparation of ethyl 2- or 3-(1-cyclopentylethylamino)benzoylacetate

A solution of 3.0 g. of tert-butyl ethyl 2- or 3-(1-cyclopentylethylamino)benzoylmalonate 10 ml. of trifluoroacetic acid is warmed with stirring for 3 hours. The solution is poured onto ice and neutralized with potassium hydroxide. The resulting precipitate is collected by filtration, washed with water and dried. Recrystallization from chloroform affords ethyl 2- or 3-(1-cyclopentylethylamino)benzoylacetate.

EXAMPLE 285

Preparation of 2- or 3-(1-cyclopentylethylamino)benzoylacetic acid

Two grams of ethyl 2-or 3-(1-cyclopentylethylamino)benzoylacetate is added to a solution of potassium hydroxide in 50 ml. of 1:9 water-ethanol. The reaction of neutralization with sulfuric acid gave a precipitate which is filtered; washed with water, and dried to yield 2- or 3-(1-cyclopentylethylamino)benzoylacetic acid.

EXAMPLE 286

Preparation of 2'- or 3'-(1-cyclopentylethylamino)-2-(methylsulfinyl)acetophenone

To a solution of 5.8 g. of dimethyl sulfoxide, dried over sieves, and 50 ml. of tetrahydrofuran is slowly added 28 ml. of n-butyllithium (2.4 M in hexane). To this mixture is added 10 g. of methyl 2- or 3-(1-cyclopentylethylamino)benzoate in 200 ml. of tetrahydrofuran. After two hours, the reaction mixture is poured onto ice, acidified with dilute hydrochloric acid and quickly extracted with chloroform. The

chloroform extract is washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Concentration affords a solid which is washed with 500 ml. of hot hexane, filtered while hot and then washed with hexane. The white solid is dried in vacuo to yield 2'- or 3'-(1-cyclopentylethylamino)-2-(methylsulfinyl)acetophenone.

EXAMPLE 287

Preparation of 2'- or 3'-(1-cyclopentylethylamino)-2-(phenylsulfonyl)acetophenone

A solution of 864 mg. of sodium hydride and 5.3 g. of methylphenylsulfone in 20 ml. of 1, 2-dimethoxyethane is stirred at 6°C. for one hour under an atmosphere of argon. To this solution is added a solution of 5.0 g. of methyl 2- or 3-(1-cyclopentylethylamino)benzoate in 50 ml. of tetrahydrofuran and the reaction mixture is stirred at 60°C. for 1.5 hours. The mixture is cooled, poured onto ice, acidified with dilute hydrochloric acid and pH 3 and then extracted with chloroform. The organic layer is separated, washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and then concentrated to dryness. The crude solid is chromatographed on silica gel, eluting with methylene chloride to yield 2'- or 3'-(1-cyclopentylethylamino)-2-(phenylsulfonyl)acetophenone.

EXAMPLE 288

Preparation of 2'- or 3'-(1-cyclopentylamino)-2-(phenylsufinyl)acetophenone

To a solution of 6.2 g. of methylphenylsulfoxide, dried over sieves, and 50 ml. of tetrahydrofuran is slowly added 28 ml. of *n*-butyllithium (2.4 M in hexane). To this mixture is added 10 g. of a solution of methyl 2- or 3-(1-cyclopentylethylamino)benzoate in 200 ml. of tetrahydrofuran. After two hours, the reaction mixture is poured into ice, acidified with diluted hydrochloric acid and quickly extracted with chloroform. The chloroform layer is washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Concentration affords a solid which is washed with 500 ml. of hot hexane, filtered while hot, and then washed with 50 ml. of hexane. The white solid is dried *in vacuo* yielding 2'- or 3'-(1-cyclopentylethylamino)-2-(phenylsulfinyl)acetophenone.

EXAMPLE 289

Preparation of 3-[2' or 3'-(1-cyclopentylethylamino)benzoyl-2,4-pentanedione

A solution of 28.4 g. of 2,4-pentanedione and 20 ml. of 1,2-dimethoxyethane is added to a suspension of 13.6 g. of sodium hydride in 220 ml. of 1,2-dimethoxyethane under argon. A solution of 28.7 g. of 2- or 3-(1-cyclopentylethylamino)benzoyl chloride hydrochloride in 1,2-dimethoxyethane is then added. The reaction mixture is stirred at room temperature for 12 hours, cooled, poured on ice and extracted with ether. The ether solution is washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated. The residue is then chromatographed over silica gel to yield 3-[2'- or 3-(1-cyclopentylethylamino)benzoyl-2,4-pentanedione.

EXAMPLE 290

Preparation of methyl 3-[2- or 3-(1-cyclopentylethylamino)benzoyl]propionate

A mixture of 35 g. of 3-(2- or 3-acetamidobenzoyl)propionic acid, 700 ml. of methanol and 1.4 ml. of concentrated sulfuric acid is refluxed for 76 hours. The solution is cooled to 35°C. and poured onto 7 g. of anhydrous sodium acetate while stirring. The reaction mixture is stirred in an ice-bath. The solid is collected and washed with cold methanol to yield methyl 3-(2- or 3-aminobenzoyl)propionate as a white solid. A mixture of this solid, 9.2 g. of 1-cyclopentylethylbromide and 4.2 g of potassium carbonate is stirred for 20 hours at 125°C. under nitrogen. The mixture is then cooled to 25°C. and 30 ml. of water is added. After stirring, the product is filtered and washed with water. Recrystallization from methanol affords methyl 3-[2- or 3-(1-cyclopentylethylamino)benzoyl]propionate as a white solid.

EXAMPLE 291

Preparation of 3-[2- or 3-(1-cyclopentylethylamino)benzoyl]propionic acid

A solution of 5.4 g. of methyl 3-[2-or 3-(1-cyclopentylethylamino)benzoylpropionate is stirred with 5.4 g. of potassium hydroxide in 100 ml. of 95% ethanol for 3 hours at reflux. The reaction mixture is cooled, diluted with 50 ml. of ethanol and 100 ml. of water, neutralized with hydrochloric acid. The solution is cooled to room temperature and filtered. The white solid is washed with 50% aqueous ethanol and dried. The product is recrystallized from ethanol to yield 3-[2- or 3-(1-cyclopentylethylamino)benzoyl]propionic acid.

TABLE XII

The following acetophenones are prepared by the noted methods from the carboxylic acids of Tables I or II or appropriate derivatives thereof which are obtained by the methods of Examples 277-280.

Example No.	Method of Example	2- or 3-(Substituted-amino)acetophenones
292	281	Diethyl 2-[(3-cyclohexylpentyl)amino]-benzoylmalonate
293	282	*tert*-Butyl ethyl 3-(1-cyclopent-3-enyl-methylamino)benzoylmalonate
294	283	Ethyl 2-[2-(cycloheptylmethylamino)-benzoyl]acetoacetate
295	284	Ethyl 3-[3-methyl-3-(4-methylcyclohex-3-enyl)propylamino]benzoylacetate
296	285	2-[3-(Cyclohex-3-enyl)propylamino]-benzoylacetic acid
297	286	3-[3-(3-Cyclohexenyl)propylamino]-2-(methylsulfonyl)acetophenone
298	287	2'-(Cyclonon-3-enylamino)-2-(phenyl-sulfonyl)acetophenone
299	288	3'-[(5-Ethylcyclohex-3-enyl)-methylamino]-2-(phenylsulfinyl)-acetophenone
300	289	3'-[2-(4-Isopropylcyclohex-2-enylamino)-benzoyl]-2,4-pentanedione
301	290	Methyl 3-[3-(2-cylooct-1-enylethyl-amino)benzoyl]propionate
302	291	3-[2-(2-Methyl-6-methylcycloheptyl-amino)benzoyl]propionic acid

EXAMPLE 303

Preparation of 2- or 3-(2-methylcyclopentylmethyl)amino]benzonitrile

2- or 3-Aminobenzonitrile (11.8g.) and 1-iodomethyl-2-methylcyclopentane (16.3 g.) are dissolved in hexamethylphosphoramide (100 ml.) and heated under nitrogen in an oil bath maintained at 120°C. for 22 hours. The reaction mixture is cooled to room temperature and water (100 ml.) is added gradually. The mixture is then chilled in an ice bath. The precipitate separated is filtered, washed thoroughly with water, and dried. It is then washed repeatedly with hexane and dried. Recrystallization from ether-hexane affords 2- or 3-(2-methylcyclopentylmethylamino)benzonitrile as pale yellow crystals.

EXAMPLE 304

Preparation of 2- or 3-(cyclohex-3-enylamino)benzaldehyde

Di-*iso*butylaluminum hydride (54 ml., 25% solution in toluene) is added with stirring to a solution of 12.1 g. of 2- or 3-(cyclohex-3-enylamino)benzonitrile under a nitrogen atmosphere. After addition is completed, the solution stirred for one hour. A solution of methanol in toluene (50 ml., 1:1) is added over 30 minutes and the mixture is poured into 500 ml. vigorously stirred ice-cold 50% aqueous sulfuric acid. The mixture is filtered and the organic layer separated. The aqueous solution is extracted twice with toluene (100 ml.) and the combined organic layers are washed with aqueous sodium bicarbonate, dried over magnesium sulfate, decolorized with charcoal, filtered and evaporated *in vacuo* to give a light yellow crystalline solid. The product is recrystallized from dichloromethane/hexane giving colorless needles.

TABLE XIII

The following 2- or 3-[(cycloalkyl or cycloalkenylsubstituted)amino, alkylamino or alkenylamino]benzonitriles are prepared by the method of Example 303.

Example No.	2- or 3-(Substituted-amino)benzonitrile
305	2-(Cyclohex-3-enylamino)benzonitrile
306	3-(Cyclohexylmethylamino)benzonitrile
307	2-(2-Methyl-6-methylenylcycloheptylamino) benzonitrile
308	3-[(4-Cyclopropyl)but-3-enylamino] benzonitrile
309	2-[1-(3-Butenyl)-2-methylcycloheptylamino] benzonitrile
310	3-[4-(2-Decahydronaphthyl)butylamino]benzonitrile
311	2-[5-(1-Cyclopentenyl)pentylamino]benzonitrile

TABLE XIV

The following 2- or 3-[(cycloalkyl or cycloalkenyl substituted amino, alkylamino or alkenylamino]benzaldehydes are prepared from the corresponding benzonitriles of Table XIII by the method of Example 304.

Example No.	2- or 3-(Substituted-amino)benzaldehydes
312	2-(Cyclohex-3-enylamino)benzaldehyde
313	3-(Cyclohexylmethylamino)benzaldehyde
314	2-(2-Methyl-6-methylenylcycloheptylamino) benzaldehyde
315	3-[(4-Cyclopropyl)but-3-enylamino] benzaldehyde
316	2-[1-(3-Butenyl)-2-methylcycloheptylamino] benzaldehyde
317	3-[4-(2-Decahydronaphthyl)butylamino benzaldehyde
318	2-[5-(1-Cyclopentenyl)pentylamino]benzaldehyde

EXAMPLE 319

Preparation of 2,3-dihydroxypropyl 2-(2-cyclohexylethylaminophenylacetate

A solution of 7.34 g. of 2-(2-cyclohexylethylamino)phenylacetic acid, 4.80 g. of 25% aqueous sodium hydroxide, and 12.6 g. of 3-iodo-1,2-propanediol in 50 ml. of hexamethylphosporamide is stirred for 24 hours at ambient temperature, diluted with 100 ml. of ether and stirred for 5 days at ambient temperature. The mixture is treated with water and extracted with ether. The dried extracts are evaporated to yield 2,3-dihydroxypropyl 2-(2-cyclohexylethylaminophenylacetic acid.

EXAMPLE 320

Preparation of methyl 3-(2-cyclohexylethylamino)phenylacetate

A solution of 20.7 g. of 3-(2-cyclohexylethylamino)phenylacetic acid in 25 ml. of hexamethylphosphoramide is added to a stirred mixture of 0.800 g. of sodium hydride (57% in mineral oil) and 25 ml. of hexamethylphosphoramide. The solution which forms after one hour is treated with 11.0 g. of methyl iodide and is then stirred at 25°C. for 18 hours. Dilution with water followed by filtration affords a white solid which is crystallized from ethanol to yield methyl 3-(2-cyclohexylethylamino)phenylacetate.

EXAMPLE 321

Preparation of 3-hydroxypropyl 2-(2-cyclohexylethylamino)phenylacetate

A mixture of 2.25 g. of methyl 2-(2-cyclohexylethylamino)phenylacetate, 280 mg. of 1,3-propanediol and 1.37 g. *p*-toluenesulfonic acid is heated at 180°C. for 18 hours and then is partitioned between ether and 3% aqueous sodium carbonate solution. The ether layer is separated, dried, and evaporated to yield 3-hydroxypropyl 2-(2-cyclo-hexylethylamino)phenylacetate.

EXAMPLE 322

Preparation of 2-ethoxyethyl 3-(cyclohex-2-enylmethylamino)phenylacetate

A solution of 11.8 g. of 3-(cyclohex-2-enylmethylamino)phenylacetic acid, 1.00 g. of 2-ethoxyethanol and 5.35 ml. of boron trifluoride etherate in 200 ml. toluene is stirred under reflux for 48 hours. The solution is treated with an additional 5.35 ml. of boron trifluoride etherate and refluxing is continued for 120 hours. Dilution with water and methylene chloride followed by filtration affords 2-ethoxyethyl 3-(cyclohex-2-enylmethylamino)phenylacetate.

EXAMPLE 323

Preparation of methyl 2-(2-cyclohexylhept-3-enylamino)hydrocinnamate

A solution of 50.5 g. of 2-(2-cyclohexylhept-3-enylamino)hydrocinnamic acid and 34.4 ml. of boron trifluoride etherate in 200 ml. of methanol is stirred under reflux for 44 hours, allowed to cool, and poured into 1.20 liters of ice-cold 5% aqueous sodium carbonate solution. The white solid is collected by filtration and recrystallized from benzene-ethanol to yield methyl 2-(2-cyclohexylhept-3-enylamino)hydrocinnamate.

EXAMPLE 324

Preparation of 1-(methoxycarbonyl)propyl 3-(cyclohex-3-enylmethylamino)hydrocinnamate

To a solution of 10.0 g. 3-(cyclohex-3-enylmethylamino)hydrocinnamoyl chloride hydrochloride in 200 ml. methylene chloride is added dropwise a solution of 3 g. methyl 2-hydroxybutyrate and 5 g. triethylamine in 100 ml. ether. After 17 hours stirring at room temperature, the precipitate is collected and washed with several portions of ether. The ether solution is washed with water, dried and evaporated to yield 1-(methoxycarbonyl)propyl 3-(cyclohex-3-enylmethylamino)hydrocinnamate as a white solid.

EXAMPLE 325

Preparation of 1-(ethoxycarbonyl)ethyl 2-(2-cyclohexylethyl amino)phenylacetate

To a warm mixture of 7 g. sodium 2-(2-cyclohexylethylamino)phenylacetate in 100 ml. ethanol is added 4.7 g. ethyl 2-tosyloxypropionate. After 17 hours at reflux, the cooled solution is diluted with an equal volume of water and the resultant precipitate is filtered. After washing with cold ethanol and drying, the product is crystallized from acetonitrile to yield 1-(ethoxycarbonyl)ethyl 2-(2-cyclohexylethylamino)phenylacetate as colorless crystals.

EXAMPLE 326

Preparation of 1-carboxyethyl 3-(2-cyclohexylethylamino)phenylacetate

A flask containing 10.0 g. 3-(2-cyclohexylethylamino)phenylacetic acid, 3.3 g. lactic acid, 500 mg. toluenesulfonic acid and 500 ml. toluene equipped with a Soxhlet extractor charged with activated 4Å Linde molecular sieves. The solution is refluxed for 24 hours during which time the Soxhlet extractor is charged twice more with fresh sieves. The hot solution is filtered and left to cool, whereupon 1-carboxyethyl 3-(2-cyclohexylethylamino)phenylacetate separates as off-white crystals.

EXAMPLE 327

Preparation of diethyl O-[2-(2-cyclohexylethylamino)phenylacetyl]tartrate

A mixture of 2-[N-trifluoroacetyl-(2-cyclohexylethylamino)]phenylacetyl chloride and 1.2 g. triethylamine in 100 ml. warm ether is treated with 2.5 g. diethyl tartrate and refluxed for 24 hours. The hot solution is filtered, the residue is washed with hot ether, and the solution is evaporated. After treatment with aqueous methanolic potassium carbonate, the product is precipitated by acidification, filtered, and dried. Crystallization from acetone yields diethyl O-[2-(2-cyclohexylethylamino)phenylacetyl]tartrate as a white, crystalline solid.

EXAMPLE 328

Preparation of O-[3-(2-cyclohexylethylamino)phenylacetyl]malic acid

A warm solution of 3-[N-carbobenzyloxy-(2-cyclohexylethylamino)phenylacetyl chloride and 1.3 g. triethylamine in 100 ml. ether is treated with 2 g. malic acid. An immediate precipitate forms, but the mixture is refluxed for one hour and filtered while hot. The solid is washed several times with hot ether, then the ether is evaporated to yield a white solid. The product is dissolved in tetrahydrofuran (100 ml.) and hydrogenated over 600 mg. 10% palladium-on-carbon at 50 psi until hydrogen uptake stops. The catalyst is filtered, and the solution is evaporated. The residue is crystallized from acetic acid to yield O-[3-(2-cyclohexylethylamino)phenylacetyl]malic acid.

EXAMPLE 329

Preparation of 2-(ethoxycarbonyl)vinyl 2-(2-cyclohexylethylamino)phenylacetate

To a mixture containing 4.3 g. 1-[2-(N-*t*-butyloxycarbonyl-2-cyclohexylethylamino)phenylacetyl]imidazole 50 ml. 5*N* sodium hydroxide is added 3 g. ethyl 2-formyl acetate. The solution is vigorously stirred for 24 hours. The layers are separated, and the chloroform solution is washed once with 50 ml. 1*N* sodium hydroxide. The solvent is evaporated and the residue is heated for 30 minutes at 40°C. in 50 ml. anhydrous trifluoroacetic acid. The solvent is again evaporated and the oil is crystallized from acetone to yield light yellow crystals of 2-(ethoxycarbonyl)vinyl 2-(2-cyclohexylethylamino)phenylacetate.

TABLE XV

The following esters are prepared by the methods shown from the carboxylic acids of Tables I, II, IV, VI, VIII and X or appropriate derivatives thereof obtained by the methods of Examples 276-280.

Example No.	Method of Example	Ester
330	319	2,3-Dihydroxypropyl 2-(1-cyclopentylethylamino)phenylacetate
331	319	2,3-Dihydroxypropyl 3-(cyclohex-2-enylmethylamino)hydrocinnamate
332	319	2,3-Dihydroxypropyl 2-(cyclooct-4-enylamino)cinnamate
333	319	2,3-Dihydroxypropyl 3-(1-allyl-2-methylcyclohexylamino)phenyl propiolate
334	319	2,3-Dihydroxypropyl 4-[2-(cyclopentyl-but-2-enylamino)phenyl]butyrate
335	320	Methyl 3-(cyclooctylmethylamino)-phenylacetate
336	320	Methyl 2-(cyclooct-2-enylamino)-hydrocinnamate
337	320	Methyl 3-(2-butylcyclopent-2-enylamino)cinnamate
338	320	Methyl 2-(cyclohex-3-enylamino)-phenylpropiolate
339	320	Methyl 4-[3-(cyclohexylmethylamino)-phenyl]butyrate
340	321	2-Hydroxypropyl 2-(3-cyclopentylpropylamino)phenylacetate
341	321	4-Hydroxybutyl 3-[(2-cyclohexyl)hex-4-enylamino]hydrocinnamate
342	321	2-Hydroxypropyl 2-(cyclopropylmethylamino)cinnamate
343	321	3-Hydroxypropyl 3-(cyclohexylmethylamino)phenylpropiolate
344	321	2-Hydroxyethyl 4-[2-(2-methylcyclohexylmethylamino)phenyl]butyrate
345	322	2-Methoxyethyl 3-(cyclohex-2-enylmethylamino)phenylacetate

346	322	2-Ethoxyethyl 2-(1-cyclopentylbut-2-enylamino)propiolate
347	323	Methyl 3-(2-cyclopentylhexylamino)hydrocinnamate
348	323	Methyl 2-(4-cycloheptylpentylamino)cinnamate
349	324	1-Methoxycarbonylpropyl 3-(cyclohexylmethylamino)hydrocinnamate
350	324	1-Ethoxycarbonylpropyl 2-[2-(cyclobutylpropyl)amino]phenylpropiolate
351	325	1-Ethoxycarbonylethyl 3-(cyclopentylmethylamino)phenylpropiolate
352	326	1-Carboxyethyl 2-(2-cyclohexylpropylamino)phenylacetate
353	326	1-Carboxyethyl 3-[2-(2-ethylcyclohexyl)ethylamino]cinnamate
354	326	1-Carboxybutyl 2-(2-cyclopentylethylamino)propiolate
355	326	1-Carboxyethyl 4-[3-(cyclopentylmethylamino)phenyl]butyrate
356	327	3-Pyridyl 2-(cyclooctylmethylamino)cinnamate
357	328	O-[3-(Cyclohexylmethylamino)benzoylmalic acid
358	328	O-[2-(4-cyclopentylbut-3-ynylamino)benzoyl]malic acid
359	329	2-(Ethoxycarbonyl)vinyl 3-(cyclohexylmethylamino)hydrocinnamate
360	329	2-(Ethoxycarbonyl)vinyl 2-(3-3cyclopentylpropylamino)cinnamate
361	329	2-(Ethoxycarbonyl)vinyl 3-(cyclohex-3-enylmethylamino)propiolate
362	329	2-(Ethoxycarbonyl)vinyl 4-[2-(1-cycloheptylpent-2-enylamino)-phenyl]butyrate

TABLE XVI

The following compounds are prepared from the carboxylic acids which may be prepared from the corresponding nitriles and aldehydes which are obtained by the methods of Examples 303 and 304 or from appropriate acid derivatives obtained by the methods of Examples 276-280.

Example No.	Method of Example	2- or 3-(Substituted-amino)compounds
363	281	Diethyl 2-(cyclooctylmethylamino)-benzoylmalonate
364	282	*tert*-Butyl ethyl 3-(2-cyclopentyl-butyl amino)benzoylmalonate
365	283	Ethyl 2-[2-(cyclopentylbut-2-enyl-aminobenzoyl]acetoacetate
366	284	Ethyl 3-[2-(2-methylcyclohexyl)-ethylamino]benzoylacetate
367	285	2-(Cyclobutylmethylamino)benzoyl-acetic acid
368	290	Methyl 3-[3-(2-cyclohexylethyl amino)benzoyl]propionate
369	291	3-[2-(2-Cyclooct-1-enylethylamino)-benzoyl]propionic acid

EXAMPLE 370

Preparation of amides

Treatment of the acids of Examples 1-186 with trifluoroacetic anhydride to provide the N-$COCF_3$ derivative, followed by treatment with thionyl chloride to provide the N-$COCF_3$ acid chloride followed by treatment with one of the following amines, followed by removal of the N-$COCF_3$ group with sodium hydroxide by the method of Example 327 provides the corresponding amides of the starting acid.

Amines: β-alanine, allylamine, allylcyclohexylamine, aminoacetonitrile, α-aminoacetophenone, 2-amino-l-butanol, 3-aminobutyric acid, 4-aminobutyric acid, l-amino-l-cyclopentanemethanol, 2-amino-5-diethylaminopentane, N-(2-aminoethyl)morpholine, N-(2-aminoethyl)piperazine, N-(2-aminoethyl)piperidine, 2-amino-2-ethyl-a,3-propanediol, 2-(2-aminoethyl)pyridine, N-(2-aminoethyl)pyrrolidine, DL-4-amino-3-hydroxybutyric acid, 5-aminolevulinic acid, aminoethanesulfonic acid, *p*-aminoethylbenzenesulfonamide, 2-amino-3-methyl-l-butanol, aminoethylcyclobutane, 4-(aminomethyl)cyclohexanecarbonitrile, l-aminoethyl-l-cyclohexanol, aminomethylcyclopropane, 4-(aminomethyl)piperidine, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl l-propanol, 2-(aminomethyl)-2-propanol, 2-aminomethylpyridine, 3-aminomethylpyridine, 4-aminomethylpyridine, 2-amino-l-phenyl-ethanol, 2-amino-3-phenyl-l-propanol, 3-amino-3-phenylpropionic acid, 3-amino-1,2-propanediol, 1-amino-2-propanol, N-(3-aminopropyl)diethanolamine, N-(3-aminopropyl) morpholine, 1-(3-aminopropyl)-2-pipecoline, N-(3-aminopropyl)-2-pyrrolidinone, 5-aminovaleric acid, bis-(2-ethanolethyl)amine, bis-(2-methylallyl)amine, *p*-bromophenethylamine, 3-bromopropylamine hydrobromide, *n*-butylamine, *sec*-butylamine, *tert*-butylamine, 2-chlorobenzylamine, 3-chlorobenzylamine, 5-chlorobenzylamine, 2-chloroethylamine, 3-chloropropylamine, cyclobutylamine, cycloheptylamine, 1, 3-cyclohexanebis(methylamine), cyclohexanemethylamine, cyclohexylamine, cyclopentylamine, cyclopropylamine, 3-(di-*n*-butylamino)propylamine, 1,5-dimethylhexylamine, α,4-di-methyl-3-hydroxyphenetylamine, 1,1-dimethylpropargylamine, 1,2-dimethylpropylamine, 1,2-diphenylethylamine, ethylamine, ethyl-3-aminobutyrate, ethyl-4-aminobutyrate, 2-(ethyl-amino)ethanol, 1-ethylpropylamine, 1-ethynylcyclohexamine, *m*-fluorobenzylamine, *p*-fluorobenzylamine, 2-fluoroethylamine, furfurylamine, *n*-heptylamine, isoamylamine, isopropylamine, *m*-methoxybenzylamine, *p*-methoxybenzylamine, 2-methoxyethylamine, *o*-methoxyphenylamine, *p*-methoxyphenylamine, N-methyl-β-alanine-nitrile, 2-methylallylamine, methylamine, methylaminoacetonitrile, 2-(methylaminoethanol, 2-methylbenzylamine, 3-methylbenzylamine, 4-methylbenzylamine, 4-methylbenzylamine, 1-methylbutylamine, 4-methylcyclohexylamine, 1-norepinephrine, 4-phenylbutylamine, 1-phenylcyclopropanemethylaine, *trans*-2-phenylcyclopropylamine, D(−)-α-phenylglycinol, 2-phenylglycinonitrile, phenylpropanolamine, 3-phenyl-a-propylamine, monopropargylamine, propylamine, taurine, tetrahydrofurfurylamine, 1,2,3,4-tetrahydro-l-naphthylamine, 2-(*p*-tolyl)ethylamine, *m*-aminobenzoic acid, *p*-aminobenzoic acid, *o*-aminobenzyl alcohol, *p*-aminobenzyl alcohol, 3,5-dimethylpiperidine, 2-ethylpiperidine, 3-hydroxypiperidine, 4-

hydroxypiperidine, 2-iminopiperidine, isonipecotamide, isonipecotic acid, methyl 4-oxo-3-piperidinecarboxylate, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, nipecotamide, 4-phenylpiperidine, 4-phenyl-1,2,3,5-tetrahydropyridine, pipecolinic acid, piperidine, 2-piperidineethanol, 2-piperidinemethanol, 3-piperidinemethanol, 4-piperidinopiperidine, 1,2,3,6-tetrahydropyridine, 2,2,6,6-tetramethylpiperidine, 2,2,6,6-tetramethyl-4-piperidinol, 4,4-trimethylenedipiperidine, 2-methylpiperidine, 3-methylpiperidine, 4-methylpiperidine, 4-phenylpiperidine, piperidine, morpholine, hexamethyleneimine, heptamethyleneimine, pentamethyleneimine, pyrrolidine, N-methylpiperazine, *dl*-alanine, hydrazine, N-acetylhydrazine, *dl*-valine, Δ^3-piperidine, *dl*-leucine, 2-aminoisobutyric acid.

EXAMPLE 371

Preparation of N-[3-(4-propylcyclohexylamino)benzoyl]benzamide

Sodium hydride (1.0 g., 50% dispersion in mineral oil) is washed with hexane three times under nitrogen. To the dry sodium hydride is added 5 ml. of freshly distilled tetrahydrofuran. To this suspension is added a solution of 2.4 g. of benzamide in 5 ml. of tetrahydrofuran. After complete reaction (30 min.), a solution of 0.9 g. 3-[N-trifluoracetyl-N-(4-propylcyclohexyl)amino]benzoyl chloride in 3 ml. of tetrahydrofuran is added. After stirring at ambient temperature for 1 hour, the reaction mixture is poured into water and extracted twice with ether. The ether extracts are washed with water, brine, dried with sodium sulfate, and concentrated *in vacuo*. The residue is recrystallized from ether-acetonitrile (1:1) to provide N-{3-[N-trifluoroacetyl-N-(4-propylcyclohexyl)amino]benzoyl}benzamide.

The N-trifluoroacetyl compound is in turn treated with ethanol and 1N sodium hydroxide and the mixture is stirred at ambient temperature for 6 hours. Chilling and filtration affords a white solid which is recrystallized from ethanol to yield N-[3-(4-propylcyclohexylamino)benzoyl]benzamide.

EXAMPLE 372

Preparation of N-[2- or 3-(substituted amino)benzoyl or phenylacetyl]benzamides

Treatment of the N-$COCF_3$ acid halides (prepared by the method of Example 278 from the corresponding acids of Examples 1-186 with benzamide and sodium hydride followed by removal of the N-$COCF_3$ group by the method of Example 371 is productive of the corresponding benzamides.

EXAMPLE 373

Preparation of 2-(cyclohexylamino)-N-(phenylsulfonyl)benzamide

A solution of 31.4 g. of benzenesulfonamide in 250 ml. of dry dimethylacetamide is added dropwise, with stirring and cooling, to a suspension of 5.5 g. of sodium hydride in 100 ml. of dry dimethylacetamide over 30 minutes at room temperature. Stirring is continued for a further 30 minutes. In the meantime, a mixture of 36.2 g. of 2-cyclohexylamino)benzoic acid in 1200 ml. of methylene chloride, 300 ml. of dimethoxyethane, and 40 ml. of thionyl chloride is refluxed for 1 hour and 15 minutes. The solution is evaporated to an oil which is co-evaporated twice with added dioxane to remove excess thionyl chloride. To the resulting oily residue of 2-(cyclohexylamino)benzoyl chloride hydrochloride is added, in one portion, the previously prepared mixture of sodium benzenesulfonamide in dimethylacetamide. The mixture is stirred for 30 minutes, without cooling, and is then filtered through a bed of diatomaceous earth. The filtrate is poured into 2 l. of water, and 250 ml. of saturated sodium chloride solution is added to coagulate the precipitate. The mixture is filtered and the product is washed with water and partially air dried. The product is dissolved in methylene chloride, the mixture is filtered through diatomaceous earth, and brine is added to break the emulsion. The layers are separated, the organic phase is dried over anhydrous sodium sulfate and filtered through a bed of 300 g. of hydrous magnesium silicate. The product is eluted with an additional 3 l. of methylene chloride. The first approximately 1 l. of filtrate is set aside and the remainder is evaporated to dryness. The residue is crystallized three times from toluene and the product is dried in the Abderhalden at 65°C. to provide the title compound as colorless crystals.

EXAMPLE 374

Preparation of 2- or 3-(substituted amino)-N-(sulfonyl)benzamides of phenylacetamides

Treatment of the acid chloride hydrochloride (prepared from the corresponding carboxylic acids of Examples 1-186 by the procedure of Example 332 with the following sulfonamides by the procedure of Example 328 is productive of the corresponding 2- or 3-(substituted amino)-N-(sulfonyl)benzamide or phenylacetamides. The sulfonamide starting materials are benzenesulfonamide, methanesulfonamide, *p*-methylphenylsulfonamide, *p*-nitrophenylsulfonamide, *p*-chlorophenylsulfonamide.

EXAMPLE 375

Preparation of methyl esters

Treatment of the acids of Examples 1-186 with excess diazomethane provides the corresponding methyl esters.

EXAMPLE 376

Preparation of hexyl esters

Treatment of the acids of Examples 1-186 with excess diazohexane provides the corresponding hexyl esters.

EXAMPLE 377

Preparation of 2- or 3-(cyclopent-3-enylamino)benzoyl chloride

A cold solution of 25 g. 2- or 3-(cyclopent-3-enylamino)benzoic acid in 500 ml. dimethoxyethane-methylene chloride (4:1) is prepared and dry hydrochloric acid is bubbled through the solution until no more precipitate forms.

The solution is treated with 25 ml. thionyl chloride and refluxed until all of the precipitate has dissolved. The solvents are evaporated to yield an orange, semi-crystalline mass.

In an analogous manner, 2- or 3-(cyclopent-3-enylamino)phenylacetyl chloride is obtained from the corresponding phenylacetic acid.

EXAMPLE 378

Preparation of N-[2-(cyclopent-3-enylamino)benzoyl]alanine

A solution pf 4.75 g. of N-trifluoroacetyl-2-(cyclopent-3-enylamino)benzoyl chloride and 1.2 g. of triethylamine in 200 ml. of warm ether is treated with 1.55 g. alanine ethyl ester and refluxed for 24 hours. The hot solution is filtered, the residue is washed with hot ether, and the solvent is evaporated from the combined filtrate and washings. After treatment of the residue with aqueous methanolic potassium carbonate, the product is precipitated by acidification, filtered and dried. Crystallization from acetone yields the product as a white, crystalline solid.

EXAMPLE 379

Preparation of 1- 3-[N-(t-butyloxycarbonyl)-N-(2-cyclopentenylamino)benzoyl imidazole

A solution of 10 g. of 3-(2-cyclopentylamino)-benzoic acid in 100 ml. dioxane is treated with 4.0 g. of *t*-butylazidoformate and 10 ml. pyridine. After stirring at room temperature for 18 hours, the protected amido-acid is precipitated from solution by addition of 150 ml. of water. The product is collected and thoroughly dried. The crude product is dissolved in 200 ml. of a mixture consisting of methylene chloride/dimethoxy ethane/pyridine (1:4:1), and to this is added 5.4 g. of 1,1'-carbonyldiimidazole. The solution is stirred overnight at room temperature and the solvents are evaporated to yield the title compound as a thick orange oil.

EXAMPLE 380

Preparation of 1-[2- or 3-(3-cyclohexenylamino)benzoyl]piperidine

To a warm solution of 2- or 3-[N-carbobenzoyloxy-3-cyclohexenylamino)benzoyl chloride and 1.3 g. of triethylamine in 100 ml. ether is added 1.2 g. of piperidine. An immediate precipitate forms, but the mixture is refluxed for one hour and filtered while hot. The solid is washed several time with hot ether, then the ether is evaporated from the combined filtrate and washings to yield a white solid. The product is dissolved in tetrahydrofuran (100 ml.) and hydrogenated over 600 mg. 10% palladium on carbon at 20 psi until hydrogen uptake stops. The catalyst is filtered. The solution is evaporated, and the residue is crystallized from acetic acid to yield the title compound as a crystalline mass.

Treatment of a corresponding 2- or 3-(substituted-amino)phenylacetyl chloride in an analogous manner yields the corresponding piperidide.

EXAMPLE 381

Preparation of 1-[2- or 3-(3-cyclohexenylamino)-benzoyl]pyrrolidine

A solution of 6.0 g. of 2- or 3-[N-carbobenzyloxy-N-(3-cyclohexenylamino)benzoyl chloride and 1.2 g. triethylamine in 100 ml. warm ether is treated with 1.1 g. of pyrrolidine. After 1 hour at reflux, the precipitate is filtered off and washed with warm ether. After evaporation of the combined filtrate and washings to dryness, the residue is dissolved in 50 ml. 30% hydrobromic acid in acetic acid and warmed at 50°C. for 2 hours. The solvents are evaporated and the product is partioned between methylene chloride and water. The layers are separated and the methylene chloride is evaported. The residue is crystallized from acetone to yield colorless crystals.

Treatment of a corresponding 2- or 3-(substituted amino) phenylacetyl chloride in an analogous manner yields the corresponding pyrrolidide.

EXAMPLE 382

Preparation of O-[2-(cyclohexylamino)benzoyl]malic acid

A warm solution of N-carbobenzyloxy-2-(cyclohexylamino)benzoyl chloride and 1.3 g. triethylamine in 100 ml. ether is treated with 2 g. malic acid. An immediate precipitate forms, but the mixture is refluxed for one hour and filtered while hot. The solid is washed several times with hot ether, then the ether is evaporated to yield a white solid. The product is dissolved in tetrahydrofuran (100 ml.) and hydrogenated over 600 mg. 10% palladium-on-carbon at 50 psi until hydrogen uptake stops. The catalyst is filtered. The solution is

evaporated and the residue is crystallized from acetic acid to yield the title compound as white crystals.

EXAMPLE 383

Preparation of N-[2- or 3-(cyclohexylamino)benzoyl]alanine

A solution of 4.75 g. of N-trifluoroacetyl-2- or 3-(cyclohexylamino)benzoyl chloride and 1.2 g. of triethylamine in 200 ml. of warm ether is treated with 1.55 g. alanine ethyl ester and refluxed for 24 hours. The hot solution is filterd, the residue is washed with hot ether, and the combined filtrate and washings are evaporated. After treatment of the residue with aqueous methanolic potassium carbonate, the product is precipitated by acidification, filtered and dried. Crystallization from acetone yields the product a white, crystalline solid.

Treatment of a corresponding 2- or 3-(substituted amino)phenylacetyl chloride in an analogous manner yields the corresponding alanines.

EXAMPLE 384

Preparation of 4-chlorophenyl 2-(3-cyclohexenylamino)benzoate

To a solution of 6.4 g. 4-chlorophenol and 7.6 g. triethylamine in 500 ml. methylene chloride is added 10.4 g. 2-(3-cyclohexenylamino)benzoyl chloride hydrochloride in 250 ml. methylene chloride. After four hours at reflux, the solution is cooled, washed with water and dilute phosphoric acid, and dried. After passing the solution through a column of alumina, the solvent is evaporated and the residue is crystallized from diisopropyl ether.

EXAMPLE 385

Preparation of N-[2-(3-cyclohexenylamino)benzoyl]-2-amino ethanesulfonic acid

To a stirred solution of 2.50 g. of taurine and 5.6 ml. of triethylamine in 22.5 ml. of water is added 5.55 g. of N- 2-[2,2,2-trifluoro-N-(3-cyclohexenyl)acetamido]benzoyloxy succinimide as a solution in 45 ml. of ethanol. After 24 hours, the mixture is treated with 20 ml. of 2.0M sodium hydroxide and 25 ml. of water. After stirring for 10 minutes, the mixture is acidified with dilute hydrochloric acid, and the crude product is collected by filtration. Recrystallization affords the title compound as a white solid.

EXAMPLE 386

Preparation of 3-[3-(3-cyclohexenylamino)benzoyl]-4-carboethoxythiazolidine

One-tenth mole of 3-(3-cyclohexenylamino)benzoyl chloride hydrochloride in methylene chloride is added to a solution of 0.1 mole of ethyl thiazolidine-4-carboxylate in chloroform containing two equivalents of triethylamine. After 5 hours at 20°C. the solution is filtered and evaporated to a white solid which is recrystallized from acetonitrile.

EXAMPLE 387

Preparation of N-[2- or 3-(cyclopentylamino)benzoyl]glycine

A mixture of 26.4 g. of ethyl N-[2- or 3-(cyclopentylamino)benzoyl]glycinate, 110 ml. of 1N sodium hydroxide solution, and 100 ml. of ethanol is stirred at ambient temperature for 2 hours and then partially evaporated. The gaseous solution is washed with diethyl ether, acidified with 6N hydrochloric acid, and filtered. The white solid is dried *in vacuo* and recrystallized from acetone.

Treatment of a corresponding 2- or 3-substituted-amino-phenylacetyl glycinate in an analogous manner yields the corresponding glycine.

EXAMPLE 388

Preparation of N-[3-(cyclopentylamino)benzoyl]-2,3-dihydroxypropylamine

To a mixture containing 4.3 g. of [N-(*t*-butyloxycarbonyl)-3-(cyclopentylamino)benzoyl]imidazole, 50 ml. of chloroform, and 50 ml. of 5N sodium hydroxide is added 1.1 g. of 3-amino-1,2-propanediol. The mixture is vigorously stirred for 24 hours, the layers are separated, and the chloroform solution is washed once with 50 ml. of 1N sodium hydroxide. The solvent is evaporated and the residue is heated for 30 minutes at 40°C. in 50 ml. of anhydrous tri-fluoroacetic acid. The solvent is again evaporated and the resulting oil is crystallized from acetone to yield the product as light yellow crystals.

EXAMPLE 389

Preparation of N-(3-bromopropyl)-2-(cycloheptylamino)benzamide

To a slurry of 21.80 g. of 3-bromopropylamine hydrobromide in 200 ml. of glyme at 3°C. is added a solution of 23.9 g. of 2-(cycloheptylamino)benzoyl chloride hydrochloride in 65 ml. of glyme, concurrently with 26 ml. of triethylamine diluted to 39 ml. with 1,2-dimethoxyethane. The solution is warmed to reflux and 0.2 g. of 4-dimethylaminopyridine is added. The solution is heated for four hours and cooled overnight. The solid is removed and the mother liquor diluted with 200 ml. of water to yield a solid which is crystallized from cyclohexane and recrystallized from acetonitrile to yield the product.

EXAMPLE 390

Preparation of 2-[3-(cycloheptylamino)phenyl]-5,6-dihydro-[4H]-1,3-oxazine

To 0.4 g. of sodium hydride in 100 ml. of 1,2-dimethoxyethane is added 2.14 g. of N-(3-bromopropyl)-3-(cycloheptyl amino)benzamide and 12 ml. of triethylamine. The turbid solution is heated to reflux for 20 hours. The solution is diluted with 100 ml. of water and cooled overnight. The solid is collected, washed with water, crystallized from cyclohexane, and recrystallized from acetonitrile to yield the product.

EXAMPLE 391

Preparation of 2-[2-(cycloheptylamino)phenyl]oxazoline

To a slurry of 15 g. of 2-bromoethylamine hydrobromide in 150 ml. of 1,2-dimethoxyethane are added simultaneously solutions of 31 g. of 2-(cycloheptylamino)benzoyl chloride hydrochloride in 60 ml. of 1,2-dimethoxyethane and 50 cc. of triethylamine (dropwise). Upon addition of 0.5 g. of 4-dimethylaminopyridine the mixture is stirred at room temperature overnight. The solution is refluxed for one hour and filtered. The solid is oven dried and partitioned between methylene chloride and water. The layers are separated and the organic phase dried over magnesium sulfate. The organic layer is concentrated and the residue collected and crystallized from cyclohexane and recrystallized from acetonitrile to yield the product.

EXAMPLE 392

Preparation of tetrahydropyranyl 3-(3-cyclohexenylamino)-benzoate

A mixture of 7 g. 3-(3-cyclohexenylamino)benzoic acid, 2 g. dihydropyran and 100 mg. anhydrous *p*-toluenesulfonic acid in 50 ml. toluene is stirred at room temperature for 20 hours. The solution is washed with saturated sodium bicarbonate, dried and evaporated. The residue is collected and crystallized from methylcyclohexane to yield the product as white crystals.

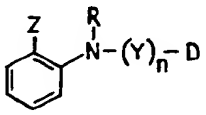
EXAMPLE 393

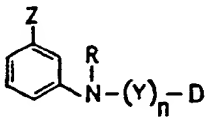
Preparation of 3 pyridyl 2-(3-cyclohexenylamino)benzoate

A 6 g. sample of 2-(3-cyclohexenylamino)benzoic acid and 2.7 g. 1,1'lcarbonydiimidazole in 50 ml. dry tetrahydrofuran is stirred for 2 hours. Then 1.58 g. 3-hydroxypyridine and a trace of soidum hydride catalyst is added and the reaction is refluxed for 3 hours. The solution cooled, filtered, and evaporated. The product is crystallized from isopropanol.

CLAIMS

1. A compound of the formula:

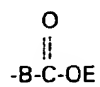




wherein Z is:

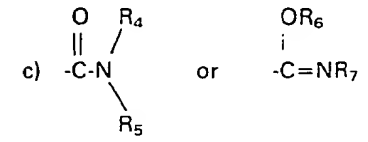
a) 

wherein A is selected from the group consisting of hydrogen, hydroxy, loweralkyl, a loweralkoxy group unsubstituted or substituted with one or more moieties selected from the group consisting of hydroxy, carboxyl, carboloweralkoxy, carboxamido, N,N-diloweralkylcarboxamido, cyano, diloweralkylamino, piperazino or polymethyleneimino (ring size 5-8) group; a benzyloxy group unsubstituted or substituted with at least one halogen or carboxy group; a phenoxy moiety unsubstituted or substituted with at least one halogen, carboxy, carboloweralkoxy loweralkyl, carboxamide, loweralkoxy or cyano group; or a 3-pyridyloxy group unsubstituted or substituted with a loweralkyl group, halogen, cyano, carboxyl, carboloweralkoxy, loweralkoxy or hydroxy group; and loweralkyl bearing one or more carboxy, carbolower-alkoxy, carbamoyl, acyl, sulfinyl or sulfonyl groups:

b) 

wherein B is saturated or unsaturated lower alkylene group and E is selected from the group consisting of hydrogen, loweralkyl, loweralkoxyethyl, diloweralkylaminoethyl, (mono or polyhydroxy)loweralkyl, (mono-

or polycarboxy)- loweralkyl, (mono- or polycarboxy)hydroxyloweralkyl, allyl, 2,3-epoxypropyl, substituted or unsubstituted (phenyl, benzyl or 3-pyridyl), pyridylmethyl, and tetrahydropyranyl; or



c) $-C(=O)-N(R_4)-R_5$ or $-C(OR_6)=NR_7$

wherein R_4 is selected from the group consisting of hydrogen, carboxyloweralkyl, carboalkoxyloweralkyl, loweralkanoyl, loweralkanesulfonyl, arylsulfonyl, sodium sulfo loweralkyl, sulfo loweralkyl, loweralkenyl, loweralkynl, phenylloweralkyl and ω-hydroxyloweralkyl; R_5 is selected from the group consisting of hydrogen, loweralkyl, hydroxy, loweralkoxy, halologweralkyl, phenyl, carboxyphenyl, chlorophenyl, sodium sulfophenyl, pyridyl, pyridyl loweralkyl, (mono- and polyhydroxy)lower alkyl, ω-loweralkoxyloweralkyl, ω-di(loweralkyl)aminoloweralkyl, ω-piperidinoloweralkyl, ω-pyrrolidinohydroxyloweralkyl, amino, loweralkanoylamino, loweralkanesulfonoylamino, N-piperidyl, arylsulfonylamino, and 4-loweralkyl-l-piperazino; R_4 and R_5 taken together with the associated nitrogen is selected from the group consisting of pyrrolidino, piperidino, morpholino, hexamethyleneimino, 4-(loweralkyl)piperidino, 4-loweralkyl-l-piperazino, 4-phenylpiperazino, 3-pyrrolinyl, Δ^3-piperidino, 4-(carboethoxy or carboxy)-3-thiazolidinyl and 4-(carboethoxy)-3-oxazolidinyl; R_6 and R_7 are the same or different and are selected from the group consisting of loweralkyl, (mono- and polyhydroxy)loweralkyl, carboxyloweralkyl, sulfo loweralkyl, sodium sulfo loweralkyl, and, when taken together, loweralkylene;

R is selected from the group consisting of hydrogen, or a group convertible *in vivo* thereinto, such as methyl, carboxymethyl, acetyl, succinyl, l-(sodium sulfo)loweralkyl, l-(sodium sulfo)polyhydroxyalkyl and 1,3-*bis*-(sodium sulfo)aralkyl;

n is either zero or one;

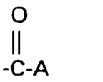
Y is a divalent radical selected from the group consisting of unbranched or branched C_1-C_{13} alkylene or alkenylene and is either unsubstituted or substituted with at least one C_1-C_4 alkyl group;

and D is selected from the group consisting of C_3-C_{16} cycloalkyl or C_4-C_{17} cycloalkenyl and is either unsubstituted or substituted with at least one C_1-C_{13} alkyl, C_4-C_8 cycloalkyl, decahydronaphthyl, methylene, ethylidene, or isopropylidene group;

with the proviso that the total number of carbon atoms in D and Y shall not exceed twenty; and with the further proviso than when n is 1, D is not an unsubstituted cyclopropyl nor a cyclopropyl substituted with at least one C_1-C_{13} alkyl;

and the pharmaceutically acceptable non-toxic acid addition and cationic salts thereof.

2. The compounds as in Claim 1 wherein R is H and Z is

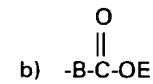


$-C(=O)-A$

wherein a is selected from the group consisting of hydrogen, hydroxy, loweralkyl, a loweralkoxy group unsubstituted or substituted with one or more moieties selected from the group consisting of hydroxy, carboxyl, carboloweralkoxy, carboxamide, N,N-diloweralkylcarboxamido, cyano, diloweralkylamino, piperazino or polymethyleneimino (ring size 5-8) group; a benzyloxy group unsubstituted or substituted with at least one halogen or carboxy group; a phenoxy moiety unsubstituted or substituted with at least one halogen, carboxy, carboloweralkoxy loweralkyl, carboxamide, loweralkoxy or cyano group; or a 3-pyridyloxy group unsubstituted or substituted with a loweralkyl group, halogen, cyano, carboxyl, carboloweralkoxy, loweralkoxy or hydroxy group; and loweralkyl bearing one or more carboxy carbolower-alkoxy, carbamoyl, acyl, sulfinyl or sulfonyl groups;

and the pharmaceutically acceptable non-toxic acid-addition and cationic salts thereof.

3. The compounds as in Claim 1 wherein R is H and Z is

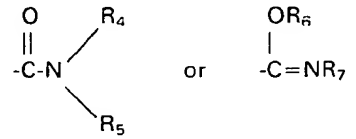


b) $-B-C(=O)-OE$

wherein B is a saturated or unsaturated lower alkylene group and E is selected from the group consisting of hydrogen, loweralkyl, loweralkoxyethyl, diloweralkylaminoethyl, (mono- or polyhydroxy)loweralkyl, (mono- or polycarboxy)-loweralkyl, (mono- or polycarboxy)hydroxyloweralkyl, allyl, 2,3-epoxypropyl, substituted or unsubstituted (phenyl, benzyl or 3-pyridyl), pyridylmethyl, and tetrahydropyranyl; or

and the pharmacologically acceptable non-toxic acid-addition and cationic salts thereof.

4. The compounds as in Claim 1 where R is H, Z is



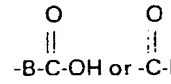
and the pharmaceutically acceptable non-toxic acid-addition and cationic salts thereof.

5. The compounds as in Claim 1 wherein R is H, Z

is -B-C-OH;

and the pharmacologically acceptable non-toxic acid-addition cationic salts thereof.

6. The compounds as in Claim 1 wherein R is H, Z is



D is C_{4-7}cycloalkyl optionally substituted or unsubstituted with up to two methyl groups; Y is C_{7-13} alkylene; n is one;
and the pharmacologically acceptable non-toxic acid addition and cationic salts thereof.

7. The compound according to claim 1, 3- 2-[1-(1,3-dimethylcyclohexyl)-2-propylamino]benzoyl propionic acid.

8. The compound according to claim 1, 3-[2-(cyclopentyl)hexylamino]benzoylacetic acid.

9. The compound according to claim 1, diethyl 2-[3-(cyclohexyl)pentylamino]benzoylmalonate.

10. The compound according to claim 1, 3-[4-(cyclohexyl)hexylamino]acetophenone.

11. The compound according to claim 1, 2-[4-(cyclohexyl)-2-ethylbutylamino]benzaldehyde.

12. The compound according to claim 1, 3'-[(2-methylcyclohexyl)methylamino]-2-(methylsulfonyl)acetophenone.

13. The compound according to claim 1, ethyl 2-[2-(1-ethylcyclohexyl)ethylamino]benzoylacetate.

14. The compound according to claim 1, 3'-[3-(4-methylcyclohexyl)propylamino]-2-(methylsulfinyl)acetophenone.

15. The compound according to claim 1, 2-[4-(4-ethylcyclohexyl)butylamino]phenylpropiolic acid.

16. The compound according to claim 1, 3-[(cyclohexyl)methylamino]cinnamic acid.

17. The compound according to claim 1, 2-[2-(cyclohexyl)ethylamino]phenylbutyric acid.

18. The compound according to claim 1, 3-[3-(cyclopentyl)propylamino]hydrocinnamic acid.

19. The compound according to claim 1, 2-[4-(cycloheptyl)butylamino]phenylacetic acid.

20. The compound according to claim 1, 2-hydropyl 3-[5-(cyclohexyl)pentylamino]phenylacetate.

21. The compound according to claim 1, carboxymethyl 2-[6-(cyclopentyl)hexylamino]phenylpropiolate.

22. The compound according to claim 1, 3-pyridyl 3-[7-(cyclopentyl)heptylamino]cinnamate.

23. The compound according to claim 1, 2-ethoxycarbonylvinyl 2-[8-(cyclohexyl)octylamino]-hydrocinnamate.

24. The compound according to claim 1, 2,3-dihydroxypropyl 3-[9-(cyclopentyl)nonyl-amino]phenylpropionate.

25. The compound according to claim 1, 2-[13-(cyclopentyl)tridecylamino]benzoic acid.

26. The compound according to claim 1, 3-[3-(cyclopentyl)cyclopentylamino]benzoylacetic acid.

27. The compound according to claim 1, 2-[3-(cyclohexyl)cyclopentylamino]phenylacetic acid.

28. The compound according to claim 1, 3-[2-(cyclopentyl)cyclopentylamino]acetophenone.

29. The compound according to claim 1, 2-[1-(cyclohexyl)cyclohexylamino]cinnamic acid.

30. The compound according to claim 1, 3-[1-(cyclopentyl)cyclopentylamino]phenylpropiolic acid.

31. The compound according to claim 1, 2-[(1-4 -methyldecahydronaphthyl)amino]hydrocinnamic acid.

32. The compound according to claim 1, 3-[2-(pentyl)cyclopropylamino]phenylacetic acid.

33. The compound according to claim 1, 2-[1-(propyl)cyclopentylamino]hydrocinnamic acid.

34. The compound according to claim 1, 3-[4-(propyl)cyclohexylamino]cinnamic acid.

35. The compound according to claim 1, 2-cyclopentylaminophenylpropiolic acid.

36. The compound according to claim 1, 3-cyclohexylaminobenzaldehyde.

37. The compound according to claim 1, 2-cycloheptylaminoacetophenone.

38. The compound according to claim 1, 3-cyclooctylaminobenzoylacetic acid.

39. The compound according to claim 1, 2-cyclodecylaminobenzoylpropionic acid.

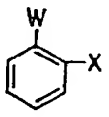
40. The compound according to claim 1, 3-cyclododecylaminophenylbutyric acid.

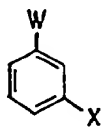
41. The compound according to claim 1, 2-[(cyclobut-2-enyl)methylamino]phenylacetic acid.

42. The compound according to claim 1, 3-[1-(cyclopent-1-enyl)propylamino]phenylbutyric acid.
43. The compound according to claim 1, 2-[1-(cyclohex-3-enyl)propylamino]hydrocinnamic acid.
44. The compound according to claim 1, 3-[1-(cyclohept-1-enyl)ethylamino]cinnamic acid.
45. The compound according to claim 1, 2-[1-cyclooct-1-enyl)ethylamino]phenylproiolic acid.
46. The compound according to claim 1, 3-[2-(2-ethyl-2-cyclopent-3-enyl)ethylamino]benzaldehyde.
47. The compound according to claim 1, 2-[2-(4-methylcyclonex-3-enyl)ethylamino]acetophenone.
48. The compound according to claim 1, 3-[2-(cyclonon-1-enylethylamino]benzoylacetic acid.
49. The compound according to claim 1, ethyl 2-[3-methyl-3-(-methylcyclohex-3-enyl)-propylamino]benzoylacetate
50. The compound according to claim 1, 3'-[(1,3,3-trimethylcyclohex-2-enyl)methylamino]-2-(methylsulfonyl)acetophenone.
51. The compound according to claim 1, diethyl 2-(cyclopent-3-enylmethylamino)benzoylmalonate.
52. The compound according to claim 1, 3'-(cyclooct-2-enyl)methylamino)-2-(methylsulfinyl)-acetophenone.
53. The compound according to claim 1,2-(cyclohept-1-enyl)methylamino)benzoylpropionic acid
54. The compound according to claim 1, ethyl 3-[13-(1-cyclopentyl)tridecylamino]benzoylacetoacetate.
55. The compound according to claim 1, ethyl 2-(4-isopropyl-cyclohex-2-enylamino)phenylacetate.
56. The compound according to claim 1, 3-(2-methylcyclooct-2-enylamino)hydrocinnamic acid.
57. The compound according to claim 1, 2-(2-methylcyclohept-2-enylamino)phenylbutyric acid.
58. The compound according to claim 1, 3-(3,7-dimethylcyclohept-3-enylamino)cinnamic acid.
59. The compound according to claim 1, 2-(cyclohept-8-enylamino)phenylpropiolic acid.
60. The compound according to claim 1, 3-(cyclopent-2-enylamino)benzaldehyde.
61. The compound according to claim 1, 2-(cyclopent-3-enylamino)acetophenone.
62. The compound according to claim 1, 3-(cyclohex-2-enylamino)benzoylacetic acid.
63. The compound according to claim 1, ethyl 2-(cyclonon-2-enylamino)benzoylacetate.
64. The compound according to claim 1, 3'-(cyclonon-3-enylamino)-2-(methylsulfonyl)acetophenone.
65. The compound according to claim 1, diethyl 2-(E-cyclodec-3-enylamino)benzoylmalonate.
66. A process for preparing compounds of Formula I as defined in Claim 1, and the pharmaceutically acceptable non-toxic acid-addition and cationic salts thereof; characterized by reacting a compound of Formula II:

$$D\text{-}(Y)_n\text{-}M \qquad \text{...II}$$

wherein M is A' or $-\overset{\overset{O}{\|}}{C}-B'$ with A' being selected from the group consisting of halogen, alkanesulfonyloxy, and arenesulfonyloxy and B' being selected from the group consisting of halogen, acyloxy, 1-imidazolyl, an activated ester moiety, hydrogen or an alkyl group of the formula C_qH_{2q+1} wherein q is an integer from 1 to 4, inclusive, selected such that the total number of carbon atoms in D, Y and C_qH_{2q+1} does not exceed twenty; with a compound of Formula III:



or


...III

wherein X is $H\text{-}\overset{\overset{R}{|}}{N}\text{-}$ or H_2N- or a group convertible *in situ* thereinto and W is Z or a precursor thereto; with the proviso that when A' is bromine and X is NH_2, A' and X may be interchanged; and when required, during or after said reaction of II with III, coverting the product to the desired I by oxidation and/or reduction of appropriate functional groups in said product;
or in any order and at any desired time before or after said reaction of compound II with compound III, converting any group or groups D, W, R, or Z to any other defined group or groups D, W, R or Z, respectively; or converting I to the corresponding pharmaceutically acceptable non-toxic acid-addition or cationic salts thereof.
67. An antiatherosclerotic composition useful for preventing or diminishing atherosclerotic lesion formation in mammals comprising a compound as defined in any one of Claims 1 - 65, and a pharmaceutically acceptable carrier or diluent therefor.
68. An antiatherosclerotic composition according to Claim 67, in dosage-unit form.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1981.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.